

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

TRISTRATA TECHNOLOGY, INC.,)	
)	
Plaintiff,)	
)	
v.)	Civil Action No.
)	
PURAC AMERICA, INC.)	
)	
Defendant.)	JURY DEMAND
)	

COMPLAINT

Plaintiff, TriStrata Technology, Inc. (“TTI”), by its attorneys, Mayer, Brown, Rowe & Maw, alleges for its Complaint against the Defendant on knowledge as to itself and its own acts and upon information and belief as to all other matters, as follows:

SUMMARY OF COMPLAINT

1. This is an action for patent infringement pursuant to the patent laws of the United States, 35 U.S.C. §100, *et seq.* arising out of Defendant’s willful and deliberate infringement of the patents described below.

2. The patents were issued to Drs. Eugene J. Van Scott and Ruey J. Yu, who are pioneers in the field of the use of alpha hydroxyacids for the treatment of conditions associated with the skin. Each of the patents describes and claims a method of using a composition containing an alpha hydroxyacid to treat and/or reduce skin conditions including but not limited to wrinkles, fine lines and other conditions affecting human skin. (The two patents at issue in this suit are collectively referred to as the “TTI Patents.”)

3. TTI provided notice of the TTI Patents to manufacturers, sellers and/or distributors of cosmetic products both in the United States and abroad. The notice explicitly informed the recipients, among other things, that: (i) the TTI Patents had been issued and

assigned to TTI; and (ii) TTI was willing to enter into a licensing agreement. To date, several of the largest manufacturers and/or marketers in the cosmetics industry have entered into such license agreements with TTI, including, without limitation, Avon, Johnson and Johnson, Chesebrough Pond's, Elizabeth Arden, Allergan, Beiersdorf, Inc., L'Oreal, Chanel, Neoteric Cosmetics, Inc., and Erno Laszlo, and TTI has received substantial royalty payments in return for granting such licenses.

4. However, Defendants have continued to refuse to recognize the TTI Patents and have willfully and deliberately infringed the TTI Patents by, among other things, promoting the use of their products through national advertisements and websites and otherwise in a manner designed to induce infringement of the TTI Patents.

JURISDICTION AND VENUE

5. This Court has jurisdiction over this action pursuant to 28 U.S.C. §§1331 and 1338(a).

6. Venue is proper in this District pursuant to 28 U.S.C. §1391(b) and (c) and 28 U.S.C. §1400(b).

THE PARTIES

The Plaintiff

7. Plaintiff TTI is a Delaware corporation with its principal place of business at 1105 North Market Street, Suite 1300, P.O. Box 8985, Wilmington, Delaware 19899. TTI is in the business of developing and licensing novel dermatological, pharmaceutical and skin care product technology. TTI is the assignee of certain patents issued to Drs. Van Scott and Yu ("the Inventors").

The Defendant

8. Defendant Purac America, Inc. (a/k/a CSM Biochemicals, hereinafter "Purac"), a subsidiary of CSM NV is an Illinois corporation with its principal place of business in Illinois. Purac is in the business of manufacturing, distributing, and/or selling cosmetic products in this District and elsewhere in the United States.

THE PATENTS

9. On August 20, 1996, United States Letters Patent No. 5,547,988, entitled "Alleviating Signs of Dermatological Aging with Glycolic Acid, Lactic Acid or Citric Acid" was duly and legally issued to the Inventors and assigned to TTI. On July 15, 1997, the PTO completed a re-examination of U.S. Patent No. 5,547,988 and issued Re-examination Certificate B1 5,547,988, in which all of the original claims were confirmed without change. A copy of this patent and its Re-examination Certificate (collectively "the '988 Patent") are annexed hereto as Exhibit A. The '988 Patent describes and claims a method for reducing the appearance of skin changes associated with aging by topically applying a composition comprising a glycolic acid, lactic acid or citric acid or a topically effective salt thereof, to the area of skin exhibiting the sign of aging.

10. On June 6, 1995, United States Letter Patent No. 5,422,370 entitled "Method of Using Lactic Acid for the Treatment of Wrinkles" was duly and legally issued to the Inventors and assigned to TTI. On July 15, 1997, the PTO completed a re-examination of U.S. Patent No. 5,422,370 and issued Re-examination Certificate B1 5,422,370, in which all of the original claims were confirmed without change. A copy of this patent and its re-examination certificate (collectively the "'370 Patent") are annexed hereto as Exhibit B. The '370 Patent describes and claims a method for visibly reducing a human skin wrinkle by topically applying a composition comprising lactic acid and/or a topically effective salt thereof, to the wrinkle.

11. TTI is the assignee of the '988 and '370 Patents.
12. TTI's methods for reducing wrinkles and other skin conditions associated with aging, as described and claimed in the annexed patents, have enjoyed excellent commercial success since their introduction. Indeed, TTI's methods have become the methods of choice for the consuming public for reducing wrinkles, fine lines and other visible effects of aging on the human skin.

FIRST CLAIM FOR RELIEF
(Infringement of the '988 Patent)

13. TTI repeats and realleges the allegations of paragraphs 1 through 12 as if fully set forth herein.
14. Purac is engaged in the manufacture, distribution and/or sale of products comprising alpha hydroxyacids, including but not limited to, lactic acid and/or a topically effective salt thereof. These products are sold and promoted over the Internet, through national advertisements, websites and/or through other marketing materials that encourage prospective customers to apply such products to their skin for the purpose of visibly reducing a human skin wrinkle and/or fine lines on the human skin.
15. By virtue of these promotional activities, Purac has been contributing to and/or inducing the infringement of the '988 Patent in violation of 35 U.S.C. §271.
16. TTI is informed and believes that Purac has received express notice of the '988 Patent and/or had prior knowledge of that patent prior to the filing of this complaint. Despite notice, Purac has failed to enter into a license agreement, and continues to contribute and/or induce infringement of the '988 Patent in violation of 35 U.S.C. §271.

17. TTI is informed and believes that Purac's actions have been willful and deliberate, entitling TTI to increased damages under 35 U.S.C. §284 and making this an exceptional case within the meaning of 35 U.S.C. §285.

SECOND CLAIM FOR RELIEF
(Infringement of the '370 Patent)

18. TTI repeats and realleges the allegations of paragraphs 1 through 35 as if fully set forth herein.

19. Purac is engaged in the manufacture, distribution and/or sale of products comprising alpha hydroxyacids, including but not limited to, lactic acid and/or a topically effective salt thereof. These products are sold and promoted over the Internet, through national advertisements, websites and/or through other marketing materials that encourage prospective customers to apply such products to their skin for the purpose of visibly reducing a human skin wrinkle and/or fine lines on the human skin.

20. By virtue of these promotional activities, Purac has been contributing to and/or to inducing the infringement of the '370 Patent in violation of 35 U.S.C. §271.

21. TTI is informed and believes that Purac has received express notice of the '370 Patent and/or had prior knowledge of that patent prior to the filing of this complaint. Despite notice, Purac has failed to enter into a license agreement, and continues to contribute and/or induce infringement of the '370 Patent in violation of 35 U.S.C. §271.

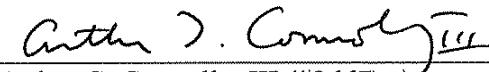
22. TTI is informed and believes that Purac's actions have been willful and deliberate, entitling TTI to increased damages under 35 U.S.C. §284 and making this an exceptional case within the meaning of 35 U.S.C. §285.

WHEREFORE, TTI prays that this Court:

- A. Find that the '988 and '370 Patents have been infringed by the Defendant, as alleged herein;
- B. Award damages adequate to compensate TTI for Defendant's infringements, but not less than a reasonable royalty for the use made of the claimed inventions by Defendant, together with interest, including pre-judgment interest, and costs as fixed by the Court;
- C. Find that Defendant's infringements have been willful and deliberate;
- D. Award TTI increased damages and attorneys' fees pursuant to 35 U.S.C. §284 and §285 because of the willful and deliberate nature of Defendant's infringements;
- E. Permanently enjoin Defendant and its officers, agents, servants, employees and affiliates, as well as all others in active concert or participation with it as any of the foregoing, from inducing or contributing to the infringement of the '988 and '370 Patents; and
- F. Award TTI such other and further relief as this Court may deem just and proper.

Dated: October 20, 2006

Respectfully submitted,



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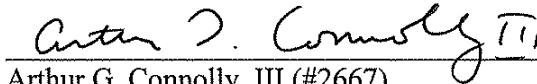
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JURY DEMAND

Plaintiff hereby demands a TRIAL BY JURY as to all issues so triable.

Dated: October 20, 2006

Respectfully submitted,



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EXHIBIT A



US005547988A

United States Patent

[19]

Yu et al.**[11] Patent Number:** **5,547,988****[45] Date of Patent:** ***Aug. 20, 1996**

**[54] ALLEVIATING SIGNS OF
Dermatological Aging With
Glycolic Acid, Lactic Acid or Citric
Acid**

[75] Inventors: **Ruey J. Yu**, Ambler; **Eugene J. Van Scott**, Abington, both of Pa.

[73] Assignee: **Stristrata Technology, Inc.**,
Wilmington, Del.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,091,171.

[21] Appl. No.: **359,939**

[22] Filed: **Dec. 20, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 117,559, Sep. 7, 1993, abandoned, which is a continuation of Ser. No. 936,863, Aug. 27, 1992, abandoned, which is a continuation of Ser. No. 683,437, Apr. 10, 1991, abandoned, which is a continuation-in-part of Ser. No. 469,738, Jan. 19, 1990, abandoned, which is a continuation of Ser. No. 945,680, Dec. 23, 1986, abandoned, and a continuation-in-part of Ser. No. 393,749, Aug. 15, 1989, Pat. No. 5,091,171.

[51] Int. Cl.⁶ **A61K 7/48**; A61K 31/19

[52] U.S. Cl. **514/557**; **514/574**; **514/844**;
..... **514/847**; **514/873**

[58] Field of Search **514/557**, **844**,
..... **514/847**, **873**, **574**

[56] References Cited**U.S. PATENT DOCUMENTS**

3,879,537	4/1975	Van Scott et al.	514/460
3,920,835	11/1975	Van Scott et al.	514/557
3,984,566	10/1976	Van Scott et al.	514/460
3,988,470	10/1976	Van Scott et al.	514/451
4,021,572	5/1977	Van Scott et al.	514/557
4,105,782	8/1978	Yu et al.	514/557
4,105,783	8/1978	Yu et al.	514/459
4,197,316	4/1980	Yu et al.	514/554
4,234,599	11/1980	Van Scott et al.	514/451
4,246,261	1/1981	Van Scott et al.	424/240
4,287,214	9/1981	Van Scott et al.	424/346
4,363,815	12/1982	Yu et al.	514/579
4,380,549	4/1983	Van Scott et al.	514/223
4,612,331	9/1986	Barratt et al.	514/558
5,091,171	2/1992	Yu et al.	424/642
5,153,230	10/1992	Jaffery	514/847
5,385,938	1/1995	Yu et al.	514/557

5,389,677	2/1995	Yu et al.	514/557
5,422,370	6/1995	Yu et al.	514/557
5,470,880	11/1995	Yu et al.	514/574

OTHER PUBLICATIONS

Hunt et al., "Anaerobic Metabolism and Wound healing . . .", *The American Journal of Surgery*, 135: pp. 328-332 (1978).

Comstock, et al., "Effect of Lactate on Collagen Proline . . .", *Proceedings of the National Academy of Science*, 66: No. 2, pp. 552-557 (1970).

Terry et al., "Implications of Heavy Chain Disease . . .", *Proceedings of the National Academy of Science*, 66: No. 2, pp. 558-563 (1970).

Cimino et al., "Ability of Nonenzymic Nitration or . . .", *Proceedings of the National Academy of Science*, 66: No. 2, pp. 564-571 (1970).

Madhanyi Chemical Abstracts No. 85:252886r, Chemical Abstracts, No. 4, p. 248, (1976).

Takahashi et al, Chemical Abstract 101:235376v (1984).

Primary Examiner—Philip I. Datlow

Attorney, Agent, or Firm—Foley & Lardner

[57] ABSTRACT

Uses of topical compositions comprising a 2-hydroxycarboxylic acid or related compound to alleviate or improve signs of skin, nail and hair changes associated with intrinsic or extrinsic aging are disclosed. 2-Hydroxycarboxylic acids and their related compounds include, for example, 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-hydroxybutane-1,4-dioicacid, 2,3-hihydroxybutane-1,4-dioic acid, 2-carboxy 2-hydroxypentane-1,5-dioic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate, ethyl 2-ketopropanoate, and gluconolactone. Topical application of compositions comprising 2-hydroxycarboxylic acid and/or related compounds has been found to alleviate or improve skin lines; blotches; blemishes; nodules; wrinkles; pigmented spots; atrophy; precancerous lesions; elastotic changes characterized by leathery, coarse, rough, dry and yellowish skin; and other skin changes associated with intrinsic aging or skin damages caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke and cigarette smoking. Topical applications of such compositions have also been found to improve the overall qualities of nail and hair affected by intrinsic aging or damaged by extrinsic factors.

14 Claims, No Drawings

5,547,988

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**ALLEVIATING SIGNS OF
DERMATOLOGICAL AGING WITH
GLYCOLIC ACID, LACTIC ACID OR CITRIC
ACID**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation of application Ser. No. 08/117,559, filed Sep. 7, 1993, now abandoned, which is a continuation of Ser. No. 07/936,863, filed Aug. 27, 1992, now abandoned, which is a continuation of Ser. No. 07/683,437, filed Apr. 10, 1991, now abandoned, which is a continuation-in-part of Ser. No. 07/469,738, filed Jan. 9, 1990, now abandoned, which is a continuation of Ser. No. 06/945,680, filed Dec. 23, 1986, now abandoned. This application is also a continuation-in-part of Ser. No. 07/393,749, filed Aug. 5, 1989, now U.S. Pat. No. 5,091,171.

FIELD OF THE INVENTION

This application relates to topical compositions containing a 2-hydroxycarboxylic acid or a related compound for use in alleviating or improving the dermatological signs of aging, including changes or damage to skin, nail and hair associated with intrinsic aging, as well as changes or damage caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, heat, dampness, chemicals, smoke, and cigarette smoking.

BRIEF DESCRIPTION OF THE PRIOR ART

In our U.S. Pat. No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoses" we described and claimed the use of topical compositions containing an alpha hydroxyacid to alleviate the symptoms of ichthyosis. In our U.S. Pat. No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of topical compositions containing an alpha hydroxyacid to alleviate the symptoms of acne. In our U.S. Pat. No. 3,984,566 entitled "Method of Alleviating the Symptoms of Dandruff" we described and claimed the use of topical compositions containing an alpha hydroxyacid to improve the symptoms of dandruff.

In our U.S. Pat. No. 4,105,783 entitled "Therapeutic Treatment of Dry Skin"; U.S. Pat. No. 4,197,316 entitled "Treatment of Dry Skin"; and U.S. Pat. No. 4,380,549 entitled "Topical Treatment of Dry Skin", we described and claimed the use of topical compositions containing an alpha hydroxyacid to alleviate or improve the symptoms of dry skin. In our U.S. Pat. No. 4,234,599 entitled "Treatment of Skin Keratoses with Alpha Hydroxyacids and Related Compounds", we described and claimed the use of topical compositions containing an alpha hydroxyacid or the related compound to alleviate the symptoms of actinic or nonactinic skin keratoses. In our U.S. Pat. No. 4,363,815 entitled "Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions", we described and claimed the use of topical compositions containing certain alpha hydroxyacids or the related compounds to improve skin conditions characterized by inflammation or disturbed keratinization.

In a report entitled "Topical Tretinoin for Photoaged Skin" by Albert M. Kligman, Gary L. Grove, Ryoji Hirose and James J. Leyden published in J. American Academy of Dermatology Vol. 15, pages 836-859, 886-887, 1986, daily topical application of 0.05% tretinoin (also known as all-trans retinoic acid) in a cream has been found to improve photodamaged skin. In another report entitled "Topical

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Tretinoin Improves Photoaged Skin: A Double-blind Vehicle-controlled Study" by Jonathan S. Weiss, Charles N. Ellis, John T. Headington, Theresa Tincoff, Ted A. Hamilton and John J. Voorhees published in J American Medical Association Vol. 259 pages 527-532, 1988, daily topical application of 0.1% tretinoin as compared to vehicle alone application for 16 weeks has been shown to improve photoaged skin. One side-effect has been a dermatitis encountered by 92% of the patients participating in this study. The

dermatitis was characterized by a patchy erythema, localized swelling, dry skin, and mild scaling. Patients complained about burning, tingling, or pruritus. In yet another report entitled "Topical Tretinoin in the Treatment of Aging Skin" by Jonathan S. Weiss, Charles N. Ellis, John T. Headington and John J. Voorhees published in J. American Academy of Dermatology Vol. 19, pages 169-175, 1988, topical application of 0.1% tretinoin cream for 8 to 12 months has been found to improve clinical signs of aging skin. The side effects have been burning sensation in the eyes and mild skin irritations.

Parent application Ser. No. 07/469,738 filed Jan. 19, 1990, now abandoned, described in addition to the main subject certain compositions containing hydroxycarboxylic acids and the related ketocarboxylic acids for topical treatment of wrinkles and skin changes associated with aging. The related application of Ser. No. 07/393,749, now U.S. Pat. No. 5,091,171 described in addition to the main subject a topical treatment to alleviate or remedy warts, nail infections, age spots, wrinkles and aging related skin changes with a composition containing certain alpha hydroxyacids or the related compounds. We have now discovered that 2-hydroxycarboxylic acids and related compounds have much broader utilization than previously disclosed.

SUMMARY OF THE INVENTION

Accordingly, it is an object of this invention to provide methods and compositions which can alleviate signs of skin, nail and hair changes associated with intrinsic and/or extrinsic aging.

We have now discovered that 2-hydroxycarboxylic acids and related compounds have unusual qualities as well as broader utilities which have not been disclosed in the prior art. Topical applications of compositions containing a 2-hydroxycarboxylic acid or a related compound have been found to improve cosmetic as well as clinical signs of changes in skin, nails and hair associated with intrinsic aging, or the damages caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and cigarette smoking. The signs of skin changes associated with intrinsic aging and the skin damages caused by extrinsic factors include thinning of skin; deepening of skin lines; wrinkles; blemishes; blotches; nodules; atrophy; pigmented spots; precancerous lesions; elastotic changes characterized by leathery, coarse, rough, dry and yellowish skin; and telangiectatic skin. The signs of nails and hair changes associated with intrinsic aging and the damages caused by extrinsic factors include thinning, fragility, splitting, lack of luster, uneven surface, and loss of flexibility and elasticity. 2-Hydroxycarboxylic acids and their related compounds which are useful for topical treatment of skin, nail and hair changes associated with intrinsic and/or extrinsic aging include, inter alia, 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-hy-

droxybutane-1,4-dioicacid, 2,3-dihydroxybutane-1,4-dioic acid, 2-carboxy 2-hydroxypentane-1,5-dioic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate, ethyl 2-ketopropanoate, and gluconolactone.

Additional objects and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and the advantages of this invention may be realized and obtained by means of the compositions and methods particularly pointed out in the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Cutaneous aging is associated with intrinsic factors with or without the additional factors of extrinsic origin. The intrinsic aging is due to internal physiologic functions and is an inherent aging process of living beings, which has not been reversible nor preventable. However, a modification, improvement or alleviation of the signs associated with cutaneous aging is now possible in accordance with this invention. Extrinsic aging, on the other hand, is due to external factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and cigarette smoking. A modification, improvement or alleviation of the signs associated with the extrinsic aging of skin, nails and hair is also now possible in accordance with this invention. Moreover, in some cases, it may be possible to eradicate such signs of intrinsic and extrinsic aging.

In the protected areas of skin such as abdomen and upper arm, the signs of skin aging which are caused by intrinsic factors include progressive thinning of skin, deepening of skin lines, wrinkles, dry and lusterless skin surface, loss of skin elasticity and recoilability. In the sun exposed areas of skin such as face and hands, the signs of intrinsic aging plus those of photoaging include deep wrinkles; marked loss of elasticity and recoilability; coarse, uneven and dry skin; blemished and leathery skin; loss of skin lubricating substances; and increased numbers of blotches, nodules and pigmented spots.

Histologically, the qualities and quantities of elastin and collagen tissues are changed. Normal elastin in tissues is replaced by abnormal elastin characterized as solar elastosis, and the normal collagen fibers are decreased.

The signs of nail and hair changes associated with intrinsic aging and the damages caused by extrinsic factors include thinning of hair and nail plate; lack of lubricants and luster, and uneven surface of hair and nails; fragility and splitting of hair and nails; and reduction of flexibility, resiliency, and elasticity of hair and nails.

The conventional management for signs of aging skin has been the use of cosmetics as well as medical procedures such as phenol, trichloroacetic acid, and other chemical peels, and plastic surgery etc. Such medical procedures are costly and risky with serious side effects, and the treatments alter only the cosmetic appearance of the skin, without any significant modifications of the underlying aging process.

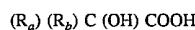
As mentioned in the previous section, recent medical reports claimed the use of topical compositions containing tretinoin to improve clinical signs of skin aging associated with intrinsic factors as well as the skin damages caused by sunlight. However, use of tretinoin has been associated with certain adverse skin reactions such as dry skin, scaling, burning, tingling, itching, erythema, skin dermatitis, localized swelling, and induction of photosensitivity.

We have now discovered that use of topical compositions containing 2-hydroxycarboxylic acid or related compounds are therapeutically effective in modification or eradication of clinical signs of cutaneous aging with minimal if any side effects or discomfort.

For convenience, the 2-hydroxycarboxylic acids and related compounds which may be used in accordance with this invention may be classified into three groups, namely (1) 2-hydroxycarboxylic acids, (2) 2-ketocarboxylic acids and esters thereof, and (3) other related compounds. The related compounds may include hydroxycarboxylic acids with the hydroxyl group at any position other than position 2, for example position 3, position 4 or position 5, as well as cyclic hydroxycarboxylic acids (e.g., ascorbic acid and quinic acid), and also may include ketocarboxylic acids and esters thereof. Preferred related compounds include 3-hydroxycarboxylic acids, and 2-ketocarboxylic acids and esters thereof.

Group 1

The first group comprises organic carboxylic acids in which one hydroxy group is attached to the 2 position carbon atom of the acid. The generic structure of such 2-hydroxycarboxylic acids may be represented as follows:



Where R_a and R_b may be the same or different and are independently selected from H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 29 carbon atoms, and in addition R_a and R_b may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. 2-Hydroxycarboxylic acids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. 2-Hydroxycarboxylic acids may exist as stereoisomers as D, L, and DL forms when R_a and R_b are not identical.

Typical alkyl, aralkyl and aryl groups for R_a and R_b include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, decyl, dodecyl, hexadecyl, benzyl, and phenyl, etc. 2-Hydroxycarboxylic acids of the first group may be further divided into subgroups comprising (1) alkyl hydroxycarboxylic acids, (2) aralkyl and aryl hydroxycarboxylic acids, (3) polyhydroxy-carboxylic acids, and (4) hydroxy-polycarboxylic acids. The following are representative 2-hydroxycarboxylic acids in each subgroup.

(1) Alkyl Hydroxycarboxylic Acids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid) (H) (H) C(OH)COOH
2. 2-Hydroxypropanoic acid (Lactic acid) (CH_3) (H) C(OH)COOH
3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid) (CH_3) (CH_3) C(OH)COOH
4. 2-Hydroxybutanoic acid (C_2H_5) (H) C(OH)COOH
5. 2-Hydroxypentanoic acid (C_3H_7) (H) C(OH)COOH
6. 2-Hydroxyhexanoic acid (C_4H_9) (H) C(OH)COOH
7. 2-Hydroxyheptanoic acid (C_5H_{11}) (H) C(OH)COOH
8. 2-Hydroxyoctanoic acid (C_6H_{13}) (H) C(OH)COOH
9. 2-Hydroxynonanoic acid (C_7H_{15}) (H) C(OH)COOH
10. 2-Hydroxydecanoic acid (C_8H_{17}) (H) C(OH)COOH
11. 2-Hydroxyundecanoic acid (C_9H_{19}) (H) C(OH)COOH
12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid) ($C_{10}H_{21}$) (H) C(OH)COOH

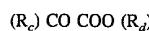
13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid) (C₁₂H₂₅) (H) C (OH) COOH
 14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid) (C₁₄H₂₉) (H) C (OH) COOH
 15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid) (C₁₆H₃₃) (H) C (OH) COOH
 16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid) (C₁₈H₃₇) (H) C (OH) COOH
 17. 2-Hydroxytetraicosanoic acid (Cerebronic acid) (C₂₂H₄₅) (H) C (OH) COOH
 18. 2-Hydroxytetraicosenoic acid (Alpha hydroxynerconic acid) (C₂₂H₄₃) (H) C (OH) COOH
 (2) Aralkyl And Aryl 2-Hydroxycarboxylic Acids
 1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid) (C₆H₅) (H) C (OH) COOH
 2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid) (C₆H₅) (C₆H₅) C (OH) COOH
 3. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid) (C₆H₅CH₂) (H) C (OH) COOH
 4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Attolactic acid) (C₆H₅) (CH₃) C (OH) COOH
 5. 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid (4-Hydroxymandelic acid) (HO—C₆H₄) (H) C (OH) COOH
 6. 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid (4-Chloromandelic acid) (Cl—C₆H₄) (H) C (OH) COOH
 7. 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid (3-Hydroxy-4-methoxymandelic acid) (HO—CH₃O—C₆H₃) (H) C (OH) COOH
 8. 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid (4-Hydroxy-3-methoxymandelic acid) (HO—CH₃O—C₆H₃) (H) C (OH) COOH
 9. 3-(2'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(2'Hydroxyphenyl) lactic acid](HO—C₆H₄—CH₂) (H) C (OH) COOH
 10. 3-(4'-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(4'Hydroxyphenyl) lactic acid](HO—C₆H₄—CH₂) (H) C (OH) COOH
 11. 2-(3',4'-Dihydroxyphenyl) 2-hydroxyethanoic acid (3,4-Dihydroxymandelic acid) (HO—,HO—C₆H₃) (H) C (OH) COOH
 (3) Polyhydroxy-carboxylic Acids
 1. 2,3-Dihydroxypropanoic acid (Glyceric acid) (HOCH₂) (H) C (OH) COOH
 2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid) (HOCH₂ HOCH) (H) C (OH) COOH
 3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid) (HOCH₂ HOCH HOCH) (H) C (OH) COOH
 4. 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid) (HOCH₂ HOCH HOCH HOCH) (H) C (OH) COOH
 5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.) (HOCH₂ HOCH HOCH HOCH HOCH) (H) C (OH) COOH
 (4) Hydroxy-polycarboxylic Acids
 1. 2-Hydroxypropane-1,3-dioic acid (Tartaric acid) (HOOC) (H) C (OH) COOH
 2. 2-Hydroxybutane-1,4-dioic acid (Malic acid) (HOOC CH₂) (H) C (OH) COOH
 3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid) (HOOC HOCH) (H) C (OH) COOH

- 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid) (HOOC CH₂)₂ C (OH) COOH
 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; saccharic acid, mucic acid etc.) HOOC (CHOH)₄ COOH

The 2-hydroxycarboxylic acids may be present in forms other than the acid, such as, for example, salts or lactones. Typical lactone forms which may be used in accordance with this invention include, for example, gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, guluronolactone, ribonolactone, saccharic acid lactone, pantothenolactone, glucoheptonolactone,mannonolactone, and galactoheptonolactone.

Group 2

The second group, which comprises compounds related to the 2-hydroxycarboxylic acids, includes organic carboxylic acids in which one keto group is attached to position 2 carbon atom of the acid. The generic structure of such 2-ketoacids may be represented as follows:



wherein R_c and R_d can be the same or different and are each selected from H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 29 carbon atoms, and in addition R_c may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for R_c and R_d include methyl, ethyl, propyl, 2-propyl, butyl, pentyl, hexyl, octyl, dodecyl, hexadecyl, benzyl and phenyl.

In contrast to 2-hydroxycarboxylic acids of the first group compounds, the ester form of 2-ketocarboxylic acids has been found to be therapeutically effective for signs and symptoms of cutaneous aging including intrinsic and extrinsic aging. For example, while methyl 2-hydroxypropanoate and ethyl 2-hydroxypropanoate have minimal effects, methyl 2-ketopropanoate and ethyl 2-ketopropanoate are therapeutically very effective. The real mechanism for such difference is not known. We have speculated that the ester form of the 2-ketocarboxylic acid is chemically and/or biochemically very reactive, and a free 2-ketocarboxylic acid may be released in the skin after penetration through the stratum corneum of the skin. The representative 2-ketocarboxylic acids and their esters of the second group are listed below:

1. 2-Ketoethanoic acid (Glyoxylic acid) (H) CO COOH
2. Methyl 2-ketoethanoate (H) CO COOCH₃
3. 2-Ketopropanoic acid (Pyruvic acid) CH₃ CO COOH
4. Methyl 2-ketopropanoate (Methyl pyruvate) CH₃ CO COOCH₃
5. Ethyl 2-ketopropanoate (Ethyl pyruvate) CH₃ CO COOC₂H₅
6. Propyl 2-ketopropanoate (Propyl pyruvate) CH₃ CO COOC₃H₇
7. 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid) C₆H₅ CO COOH
8. Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate) C₆H₅ CO COOCH₃
9. Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate) C₆H₅ CO COOC₂H₅

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10. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid) C₆H₅CH₂ CO COOH
11. Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate) C₆H₅CH₂ CO COOCH₃
12. Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate) C₆H₅CH₂ CO COOC₂H₅
13. 2-ketobutanoic acid C₂H₅ CO COOH
14. 2-Ketopentanoic acid C₃H₇ CO COOH
15. 2-Ketohexanoic acid C₄H₉ CO COOH
16. 2-Ketoheptanoic acid C₅H₁₁ CO COOH
17. 2-Ketoctanoic acid C₆H₁₃ CO COOH
18. 2-Ketododecanoic acid C₁₀H₂₁ CO COOH
19. Methyl 2-ketoctanoate C₆H₁₄ CO COOCH₃

Group 3

The third group, which also comprises related compounds, includes, inter alia, hydroxycarboxylic acids where the hydroxy is at a position other than position 2, and cyclic hydroxycarboxylic acids which are useful for topical application to improve signs of aging skin and the cutaneous appendages. The members of this group, which are more conveniently identified by name than by generic structures, include ascorbic acid, quinic acid, isocitric acid, tropic acid (2-phenyl 3-hydroxypropanoic acid), trethocanic acid, 3-chlorolactic acid, citramalic acid, agaricic acid, aleuritic acid, pantoic acid, lactobionic acid and hexulosonic acid.

Amplifying Bioactivities of Cosmetic and Pharmaceutical Agents

The compositions of present invention may contain one or more 2-hydroxycarboxylic acids or related compounds to magnify the therapeutic effect of an unrelated cosmetic or pharmaceutical agent. At least one compound selected from the group consisted of 2-hydroxycarboxylic acids and related compounds may be incorporated into a composition containing a cosmetic or pharmaceutical agent for topical treatment to improve or alleviate signs of skin, nails or hair changes associated with intrinsic aging or the damages caused by extrinsic factors. It has been found that such incorporation have resulted in magnified therapeutic efficacies which are not simply additive effects.

Most pharmaceutical drugs produce their therapeutic effects by first interacting with their receptors in the target tissues. Many drug receptors are functional macromolecules such as enzymes, cell membrane components or certain components of cells. The binding affinity or interacting property of a drug toward its specific receptor molecule is intimately governed by the chemical structure of the drug. Since most pharmaceutical agents are chemically different from 2-hydroxycarboxylic acids and related compounds, the respective receptor molecules should be different and so are the pharmacologic actions and the therapeutic effects. Under such conditions if 2-hydroxycarboxylic acid or a related compound is incorporated into a composition containing a pharmaceutical agent, one of the following two consequences may arise:

(a) No enhancement or any substantial changes in either effect. In this case, the overall clinical effect would be a mixing effect, i.e. the effect due to the pharmaceutical agent alone mixed with the effect due to the 2-hydroxycarboxylic acid or the related compound alone. Also in this case, the interaction between the pharmaceutical agent and its receptor molecule is not affected nor interfered by the presence of

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2-hydroxycarboxylic acid or the related compound. Nor does 2-hydroxycarboxylic acid or the related compound assist in or enhance the binding affinity or the interaction of the pharmaceutical agent toward its receptor molecule. The clinical results from such combination composition would be just the mixing effects, and are predictable.

(b) Amplified therapeutic action or substantial loss of therapeutic action in either effect. In this case, the interaction between the pharmaceutical agent and its receptor molecule is affected either positively or negatively by the presence of 2-hydroxycarboxylic acid or the related compound. From the point of positive effect, 2-hydroxycarboxylic acid or the related compound may produce an amplified effect by either increasing the affinity of the receptor molecule toward the pharmaceutical agent; acting as a better and more efficient coenzyme or as an activator by disrupting barriers and removing obstacles for better binding of the agent toward its receptor molecule; for example, enzyme activation by removal of natural inhibitors. In all these cases the overall clinical results would be due to magnified therapeutic effects which are not predictable from either effect alone.

From the point of negative effect, a 2-hydroxycarboxylic acid or a related compound might interfere with or decrease the binding affinity of the pharmaceutical agent toward its receptor molecule; i.e. acting as an inhibitor. In such case, the overall clinical results should be due to a substantial diminishment or completely loss of therapeutic effects, which is also unpredictable from either effect alone.

We have found that, in most cases, therapeutic effects of cosmetic and pharmaceutical agents are amplified when a 2-hydroxycarboxylic acid or a related compound is incorporated into the composition, i.e., consequence (b) above is observed.

The cosmetic and pharmaceutical agents which may be actuated by 2-hydroxycarboxylic acids or related compounds include those that improve or eradicate age spots, keratoses and wrinkles by different mechanism of action; antimicrobial and antiacne agents; antipruritic and antix-erotic agents; antiinflammatory agents; sunscreen and antiphotosensitive agents; nail and hair conditioners, cleansers, care and treatment agents; wart removers; skin lightening agents; depigmenting agents; local anesthetics and analgesics; corticosteroids; retinoids; vitamins; hormones; and antimetabolites.

Some examples of cosmetic and pharmaceutical agents include acyclovir, amphotericins, chlorhexidine, clotrimazole, ketoconazole, miconazole, metronidazole, minocycline, nystatin, neomycin, kanamycin, phentytoin, octyl dimethyl PABA, octyl methoxycinnamate, PABA and other esters, octyl salicylate, oxybenzone, dioxybenzone, tocopherol, tocopheryl acetate, selenium sulfide, zinc pyrithione, soluble elastin, diphenhydramine, pramoxine, lidocaine, procaine, erythromycin, tetracycline, clindamycin, hydroquinone and its monomethyl and benzyl ethers, naproxen, ibuprofen, cromolyn, retinoic acid, retinol, retinyl palmitate, retinyl acetate, coal tar, griseofulvin, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, minoxidil, dipyridamole, diphenylhydantoin, benzoyl peroxide and 5-fluorouracil.

Specific Compositions For Skin And Skin Appendages

While 2-hydroxycarboxylic acids and related compounds are therapeutically effective for topical treatment to improve

or alleviate signs of skin, nail or hair changes associated with intrinsic aging and/or photoaging, certain compounds of the instant invention are more potent than others. In selecting a particular compound of the present invention two factors, namely (a) potency and (b) concentration have to be considered. If rapid results are preferred in certain cases, most potent compounds with highest and safe concentrations may be used. Under such conditions the treatment time is substantially shortened with good to excellent clinical results. Generally, such treatment has to be carried out under supervision by a dermatologist or trained professional in the office, medical center, skin care center, or beauty salon etc. Such procedure or treatment may include micro and semimicro peels, epidermolysis or superficial peel, and dermolysis or deeper peel.

Examples of more potent 2-hydroxycarboxylic acids and related compounds to be formulated in specific compositions include 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate. The concentration of 2-hydroxycarboxylic acid or the related compound used in such specific composition may range from an intermediate to a full strength, therefore the dispensing and the application require special handling and procedures.

If the 2-hydroxycarboxylic acid or the related compound at full strength (usually 85–100%) is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent is directly dispensed as 0.5 to 1 ml aliquots in small vials.

If the 2-hydroxycarboxylic acid or the related compound at full strength is a crystalline or solid form at room temperature such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid, the crystalline or solid compound is first dissolved in a minimal amount of vehicle or vehicle system prepared from water, ethanol, propylene glycol and/or butylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used 0.1 to 2% of hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose, chitosan, carbomer, or polyquaternium-10 may be incorporated into the above solution.

To formulate an intermediate strength (usually 20–50%), 2-hydroxycarboxylic acid or the related compound either a liquid or solid form at room temperature is first dissolved in a vehicle or vehicle system prepared from water, acetone, ethanol, propylene glycol and/or butylene glycol. For example, 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is dissolved in ethanol 56 g and propylene glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

General Preparation of Compositions

Most compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, or other pharmaceutically acceptable form. To prepare a composition in solution form for general use, at least one 2-hydroxycarboxylic acid or related compound is dissolved in a solution prepared from ethanol, water, propylene glycol, butylene

glycol, acetone or other pharmaceutically acceptable vehicle. The concentration of the 2-hydroxycarboxylic acid or related compound may range from 0.1 to 100 percent, the preferred concentration ranges being from about 2 to about 25 percent for home use, with higher ranges, e.g., from about 70 to about 100 percent being acceptable for office use where professional supervision is provided. Thus, such concentrations can also range from about 25 to about 50 percent and from about 50 to about 70 percent, with the proviso that concentrations of about 25 percent or more generally requiring profession supervision.

In the preparation of a composition in lotion, cream or ointment form, at least one of 2-hydroxycarboxylic acids or related compounds is initially dissolved in a solvent such as water, ethanol, butylene glycol, and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of 2-hydroxycarboxylic acids or related compounds used in the compositions are the same as described above.

Thin gel compositions are specifically useful for topical application to hair and face. A typical gel composition of the instant invention is formulated by dissolving at least one of 2-hydroxycarboxylic acids or related compounds in a vehicle prepared from ethanol, water, butylene glycol, and/or propylene glycol. A gelling agent such as xanthan gum, polyquaternium-10, methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, chitosan, hydroxypropylmethylcellulose, ammoniated glycyrrhizinate or carbomer is then added to the solution with agitation. The preferred concentration of the gelling agent may range from 0.1 to 2 percent by weight of the total composition.

To prepare an actuated composition, a cosmetic or pharmaceutical agent is incorporated into any one of the above formulations by dissolving or mixing the agent into the composition.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limited. Therefore, any of the aforementioned 2-hydroxycarboxylic acids and related compounds may be substituted according to the teachings of this invention in the following examples.

EXAMPLE 1

A typical solution composition containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows. 2-Hydroxyethanoic acid (glycolic acid) crystals 7 g is dissolved in water 50 ml and propylene glycol 15 ml. Ethanol is added to the solution until the total volume is 100 ml. The composition thus prepared contains 7% w/v 2-hydroxyethanoic acid.

EXAMPLE 2

A typical gel composition containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

2-Hydroxypropanoic acid (DL-lactic acid) USP grade 5 g is dissolved in water 60 ml and butylene glycol 10 ml, and chitosan or polyquaternium-10 0.3 g is added with stirring. Ethanol is added to the mixture until the volume is 100 ml. The mixture is stirred until a uniform gel is obtained. The thin gel thus obtained contains 5% 2-hydroxypropanoic acid.

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11**EXAMPLE 3**

A typical oil-in-water emulsion containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

2-Methyl 2-hydroxypropanoic acid (methylactic acid) crystals 10 g is dissolved in water 20 ml and concentrated ammonium hydroxide 2 ml is added to the solution. The solution is mixed with enough hydrophilic ointment USP to make a total weight of 100 g. The cream thus formulated contains 10% 2-methyl 2-hydroxypropanoic acid.

EXAMPLE 4

A typical water-in-oil emulsion containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

Glucolonolactone 7 g is dissolved in water 12 ml and concentrated ammonium hydroxide 0.5 ml is added to the solution. The solution is mixed with enough water-in-oil emulsion to make a total weight of 100 g. The water non-washable cream thus formulated contains 7% gluconolactone.

EXAMPLE 5

A typical ointment containing 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid (mandelic acid) crystals 10 g is dissolved in 10 ml ethanol, and the solution thus formed is mixed with mineral oil 35 g and enough white petrolatum to make a total weight of 100 g. The ointment thus formulated contains 10% 2-phenyl 2-hydroxyethanoic acid.

EXAMPLE 6

A specific preparation containing a full strength or a high concentration of 2-hydroxycarboxylic acid or the related compound may be formulated and dispensed as follows.

If 2-hydroxycarboxylic acid or the related compound at full strength is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the compound is directly dispensed as 0.5 to 1 ml aliquots in small vials. If the compound is a crystalline or solid form, such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid and 2,2-diphenyl 2-hydroxyethanoic acid, the compound is first dissolved in minimal amount of an appropriate vehicle system selected from water, ethanol, propylene glycol and butylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 ml, and 70% strength 2-hydroxyethanoic acid with or without addition of 0.5% chitosan or polyquaternium-10 is dispensed as 1 to 5 ml aliquots in small vials.

EXAMPLE 7

A typical preparation containing an intermediate strength of 2-hydroxycarboxylic acid or the related compound may be formulated as follows.

Malic acid, tartaric acid or citric acid 35 g is dissolved in water 60 ml and propylene glycol 5 ml. The 35% strength solution thus prepared is dispensed as 5 to 10 ml aliquots in dropper bottles.

12**EXAMPLE 8**

A composition containing 2-hydroxycarboxylic acid or the related compound to magnify the therapeutic effect of a cosmetic or pharmaceutical agent for wrinkles and other signs of skin aging may be formulated as follows.

Ethyl 2-ketopropanoate (ethyl pyruvate) 2 g and all-trans retinoic acid 0.02 g are dissolved in a vehicle system prepared from ethanol 50 ml, water 28 ml and propylene glycol 20 ml. The composition thus formulated contains retinoic acid 0.02% and ethyl 2-ketopropanoate 2%.

EXAMPLE 9

A composition containing 2-hydroxycarboxylic acid or the related compound to amplify the therapeutic effect of a dermatologic agent for blemishes, pigmented spots and wrinkles may be formulated as follows.

2-Hydroxyethanoic acid 8 g, hydroquinone 2 g and sodium metabisulfite 0.4 g are dissolved in a vehicle prepared from ethanol 30 ml, water 45 ml and propylene glycol 15 ml. Chitosan or polyquaternium-10 0.3 g is added to the solution with stirring. The mixture is stirred until a uniform gel is obtained. The thin gel thus obtained contains hydroquinone 2% and 2-hydroxyethanoic acid 8%.

EXAMPLE 10

A typical cleansing and soothing composition containing 2-hydroxycarboxylic acid or the related compound to enhance the therapeutic effect of a dermatologic agent for initial treatment of hair or skin changes associated with aging may be formulated as follows.

2,2-Diphenyl 2-hydroxyethanoic acid (benzilic acid) 2 g and chlorhexidine 0.3 g are dissolved in a vehicle system prepared from ethanol 30 ml, water 58 ml and butylene glycol 10 ml. The solution thus formulated contains chlorhexidine 0.3% and 2,2-diphenyl 2-hydroxyethanoic acid 2%.

EXAMPLE 11

A typical lotion containing 2-hydroxycarboxylic acid or the related compound to substantiate and magnify the sunscreen effect of a dermatologic agent may be formulated as follows.

2-Hydroxyethanoic acid 3 g and concentrated ammonium hydroxide 0.75 ml are dissolved in water 7 ml, and the solution thus obtained is mixed with 85 g of an oil-in-water emulsion which contains octyl methoxycinnamate 5 g. The actuated sunscreen lotion thus formulated contains 5% sunscreen agent and 3% 2-hydroxyethanoic acid.

TEST RESULTS**(1) Biologic and Pharmacologic Actions**

The skin may be classified into two major parts; dermis and epidermis. The dermis contains blood vessels, nerves, collagen, elastin etc, and fibroblast cells in the dermis are responsible for the biosynthesis of collagen and elastin. The epidermis contains nerves but no collagen, elastin, nor blood vessels.

The epidermis is further divided into two distinct zones; malpighian layer and horny layer. The malpighian layer, a living tissue, is further divided into basal, spinous, and granular layers. The horny layer, a dead tissue, is also called stratum corneum. In the natural process, basal cells in the

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basal layer move outward through the spinous and granular layers to become dead cells called corneocytes, in the stratum corneum. The stratum corneum consists of approximately 14 layers of corneocytes. In normal skin it takes about 14 days for the basal cells to move from the basal layer to the end of the granular layer and to become corneocytes, and another 14 days to reach the outermost layer of the stratum corneum. This process of forming corneocytes is called keratinization, and stratum corneum, nail, and hair are the natural products produced by such process. The stratum corneum is the skin tissue that one feels when touching the skin. Usually, it takes about 28 days for cells of the basal layer to move outward to the surface in the course of making new skin.

We have found that compositions containing low concentrations of 2-hydroxycarboxylic acid or the related compound, when applied topically to the skin, diminish corneocyte cohesion in the stratum corneum. This effect predominantly occurs among corneocyte cells at inner levels of the stratum corneum, i.e. near the junction to the granular layer, and there is no effect among corneocyte cells at outer layers in the stratum corneum. Therefore, 2-hydroxycarboxylic acids and related compounds are not typical kertolytics such as strong acids, strong alkalis, thiols, urea and lithium salts which cause disaggregation of corneocyte cells in the outer layers of the stratum corneum.

We have also discovered that compositions containing intermediate to high concentrations of 2-hydroxycarboxylic acid or the related compound, when topically applied to the skin, cause profound beneficial effects in the dermis as well as the epidermis of the skin. The skin becomes thicker and plump as measured clinically by caliper and micrometer techniques. Histometric techniques using microscopic analysis of tissue biopsy specimens confirm that new and more collagen and elastic fibers have been biosynthesized in the dermis.

The biologic and pharmacologic actions of 2-hydroxycarboxylic acid or the related compound suggest that topical application of the composition should improve or alleviate signs of skin, nail, and hair changes associated with intrinsic and/or extrinsic aging.

(2) Therapeutic Effects

In order to determine whether compositions containing 2-hydroxycarboxylic acid or the related compound were therapeutically effective for topical application to improve or alleviate signs of skin, nail, and hair changes associated with intrinsic and/or extrinsic aging, a total of more than 120 volunteers and patients participated in these studies. Intrinsic aging is due to internal physiologic process, different from the damage caused by an external factor such as sunlight. The body areas showing predominantly intrinsic aging are in the protected regions of the skin such as abdomen, buttock, and upper arm. The signs of intrinsic aging include thinning of skin, deepening of natural skin lines, fine wrinkles, dry and lusterless skin surface, loss of skin elasticity and recoilability. Therefore, for intrinsic aging test compositions were topically applied to the skin of upper arms and/or abdomen.

The extrinsic aging is a progressive damage caused by environmental factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and/or smoking. The body areas predominantly involved are in the exposed regions of the skin such as face, scalp with thin or no hair, neck, forearms, and the back of hands. The signs of

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extrinsic aging in these skin areas are in most cases a combination of intrinsic aging and extrinsic aging unless it involves a very young person. The signs of both intrinsic and extrinsic aging include fine and deep wrinkles, loss of elasticity and recoilability, coarse and very dry skin, blemished and leathery skin, loss of skin lubricants, and increased numbers of age spots, blotches, nodules and pigmented spots. In such cases test compositions were topically applied to face, forearms, and the back of hands.

The composition containing a weak to intermediate concentration of 2-hydroxycarboxylic acid or the related compound was topically applied to the skin by a patient or a participating subject at home, as a home treatment. The composition containing a high concentration or a full strength of 2-hydroxycarboxylic acid or the related compound was topically applied to the involved skin of a patient, such as the face, by a dermatologist or a trained health professional as an office procedure or treatment. For rapid therapeutic results, both home and office treatments were adopted in many cases.

(a) Home Treatment

In order to determine whether the composition containing a 2-hydroxycarboxylic acid or related compound was therapeutically effective for topical application to alleviate or improve signs of skin changes associated with intrinsic and extrinsic aging on the face or the back of hands, both patients and volunteer subjects were included in the study. The compositions containing 5 to 30%, and preferably between 8 to 20%, of a 2-hydroxycarboxylic acid or related compound were formulated with optimal bioavailability of the active ingredient according to the examples. The participants were instructed to apply the compositions twice daily on the face and the back of hands for intervals of 2 to 12 months. All participants were instructed to avoid sun exposure, and to use a sunscreen product with a sun protection factor of 15 or greater if exposure to sunlight was unavoidable.

Photographs of each side of the face, and the back of hands were taken at the beginning of the study and repeated at one to three-month intervals. The participants were asked not to wear facial makeup nor to apply any products on the back of hands at the time of the visit, except for eye shadow if desired. Standardized photographic conditions were used: the same light source at two feet from the face aimed at a locus on the frontal aspect of each cheek, and also at two feet from the back of hands. Photographs were taken with the camera aimed perpendicular to the cheek or the back of hands.

After 2 months of home treatment all of a group of 35 participants showed substantial improvement of the face and the back of hands. The skin was smoother, glossy, and softer. Blotches, blemishes, and age spots on the face were also decreased in number or were lighter in color in a group of 30 out of 35 closely monitored participants. After 6 to 9 months of continued home treatment, skin lines and fine wrinkles on the face either disappeared or were diminished in 24 out of this group of 35 participants. Great numbers of age spots and blemishes on the face and the back of hands also continued to disappear or become much less conspicuous. The skin appeared and felt smooth, soft, and glossy. Coarser wrinkles were substantially reduced after 18 months of continued home treatment.

(b) Office Treatment

Specific compositions containing a high concentration to a full strength of a 2-hydroxycarboxylic acid or related compound were used in most cases as an office procedure or

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treatment. The composition containing 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-ketopropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, or 2,2-diphenyl 2-hydroxyethanoic acid at concentrations of 50% or higher was prepared according to the examples.

The composition was topically applied to the skin and gently massaged in with the fingers or a cotton ball by a dermatologist or a trained health professional who wore rubber gloves. After 1 to a few minutes, depending on the strength used and the skin sensitivity of the subject, the skin was gently rinsed with water.

Such office treatment was repeated every 2 to 3 weeks. Photographs of the skin so treated were taken at the beginning of the study and repeated at one to three-month intervals as described in the previous section.

After one to two office treatments, all 32 patients in this particular study showed distinct improvement of the face and other areas treated, such as the forearms, the back and the back of hands. The original coarse, rough, and dry skin had improved markedly, and the skin was smooth, glossy, and soft. The number of blotches, blemishes, brownish spots, and age spots decreased significantly after 3 to 5 office treatments. Facial skin lines and fine wrinkles improved or disappeared in 25 out of this group of 32 patients after 8 to 12 office treatments.

(c) Office Treatment Plus Home Treatment

If rapid therapeutic results are desired, home treatment may be combined with the office treatment. After each office treatment, the patient would topically apply twice daily a composition containing a low to intermediate concentration of a 2-hydroxycarboxylic acid or related compound on the face and the back of hands.

After one office treatment plus twice daily home treatment, all 28 patients of this study showed marked improvement on the texture of treated skin. The rough, coarse, and dry skin disappeared, and the skin was smooth, glossy, and soft after one month. Blotches, blemishes, nodules, age spots, pigmented spots, skin lines, and fine wrinkles improved or disappeared, 3 to 5 months after the office treatment plus the home treatment. Deep wrinkles started to improve visibly as measured by photographic means after 5 to 10 months of sustained office treatments and continued home treatments.

Most patients showed marked improvement of deep wrinkles after 12 to 18 months of combined office and home treatments.

(d) Epidermolysis and Dermolysis

While the office procedure described in the previous section causes a micro or semimicro peeling of the skin, procedures which cause epidermolysis and dermolysis result in superficial and deeper peeling of the skin. When a composition containing a high concentration or a full strength of a 2-hydroxycarboxylic acid or related compound such as 70% 2-hydroxyethanoic acid, 85% 2-hydroxypropanoic acid, and 100% 2-ketopropanoic acid is topically applied to a photodamaged skin, epidermolysis will occur if the time of contact with the skin is long enough. The epidermolysis is clinically beneficial for topical treatment of acne, age spots, keratoses, pigmented spots, skin lines, blemishes, wrinkles and other signs of skin changes associated with intrinsic and extrinsic aging.

In general, epidermolysis of skin occurs faster on the face than on the upper back or the back of hands, and faster on skin of younger people than of older people and usually

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faster in women than men. The clinical sign of epidermolysis is blanching of the skin, a sign that signals the threshold between superficial peeling and deeper peeling. When blanching of the skin is first seen the skin is immediately rinsed with water to prevent a deeper peeling of the skin.

In dermatologic practice dermolysis or deep peeling has been induced for the treatment of blemished skin or aging skin by using peeling agents such as trichloroacetic acid and phenol. These peeling agents are very caustic to the skin and are also toxic. Serious side effects including death have been reported. A 2-hydroxycarboxylic acid or related compound can be safely used as a micro, semimicro, superficial or deep peeling agent for topical treatment of dermatologic disorders including skin changes associated with intrinsic aging or skin damages caused by extrinsic aging such as photoaging.

The face of a patient to be so treated was initially wiped with 70% ethanol, and the eyes were covered with wet cotton balls. A full strength (100%) 2-ketopropanoic acid, or an aqueous solution containing 70% 2-hydroxyethanoic acid or 85% 2-hydroxypropanoic acid was uniformly applied to the skin using a cotton ball. The patient usually feel a transient burning sensation. Erythema usually appeared after less than a minute up to a few minutes depending on the skin type, age, sex etc. The skin was rinsed with water after blanching of the skin occurred or intense erythema persisted.

A total of 23 patients participated in the epidermolysis study. Most participants also daily used emollient lotions or creams containing weak concentrations of a 2-hydroxycarboxylic acid or related compound. All the participants showed marked improvement of skin lines, blemishes and fine wrinkles after 2 months.

(3) Amplified Bioactivities

We have discovered that when a 2-hydroxycarboxylic acid or related compound is incorporated into a composition containing a dermatologic agent, the pharmacologic actions and the therapeutic effects are unexpectedly amplified in most cases. For example, a 2-hydroxycarboxylic acid or related compound magnifies the therapeutic effects of hydroquinone, 5-fluorouracil, chlorhexidine, clotrimazole, miconazole, tetracycline, retinoic acid etc. Compositions containing 2-hydroxycarboxylic acid or the related compound and a dermatological or other pharmaceutical agent were formulated according to the examples.

Each participating patient received two compositions; i.e. with or without the incorporation of a 2-hydroxycarboxylic acid or related compound. The patients were instructed to apply topically one medication on one side of the body such as on the back of the left hand and the other medication on the other side of the body such as on the back of the right hand. Specific instructions were given to the patients to apply the medications twice daily to the involved areas or lesions of blemishes, age spots, melasma, lentigines, skin lines, wrinkles, or precancerous actinic keratoses. Clinical improvements were discernible after a few weeks to a few months of topical application. The sides treated with amplified compositions were substantially better than the sides treated with the medications which did not contain any 2-hydroxycarboxylic acid or the related compound.

(4) Hair and Nail Treatments

Compositions containing a 2-hydroxycarboxylic acid or related compound at low concentrations, preferably from 1 to 4%, for hair care and treatment were formulated according to the examples. A solution or thin gel form thus formulated

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was topically applied to the hair after shampoo. The same treatment was repeated 3 to 4 times weekly. After a few weeks to a few months of such treatment, the signs of hair changes associated with intrinsic aging and the damages caused by photoaging started to improve substantially. The hair first appeared smooth and shiny. The hair became softer to the touch and feel. After a few months of such treatment, hair increased its elasticity and flexibility.

Compositions containing 2-hydroxycarboxylic acid or the related compound at intermediate concentrations, preferably from 8 to 20%, for nail care and treatment were formulated according to the examples. A solution or thin gel form thus prepared was topically applied twice daily to edges, surface and base of affected nail plates. After a few months of such treatment, the signs of nail changes associated with intrinsic and extrinsic aging started to improve noticeably. The nail looked glossy and felt smooth on the surface. The flexibility and elasticity of the nail after the treatment also increased. Brittleness diminished and the occurrence of terminal nail splitting became rare.

It will be apparent to those skilled in the art that various modifications and variations can be made to the compositions of matter and methods of this invention. Thus, it is intended that the present invention covers such modifications and variations.

What is claimed is:

1. A method for reducing the appearance of skin changes associated with intrinsic and/or extrinsic aging, said skin changes associated with aging resulting from natural or innate aging or exposure to actinic radiation,

whereby said skin changes associated with aging are selected from the group consisting of wrinkles, thinning of the skin, deepening of skin lines, yellowish skin, loss of elasticity, loss of recoilability, and loss of collagen,

said method comprising topically applying to an area of skin exhibiting said change a composition comprising a compound selected from the group consisting of glycolic acid, lactic acid, citric acid, or a topically

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effective salt thereof, in an amount and for a period of time sufficient to reduce the appearance of said skin changes associated with aging.

2. The method of claim 1, wherein said extrinsic aging is caused by extrinsic factors selected from the group consisting of sunlight; radiation; air pollution; wind; cold; dampness; heat; chemicals; smoke; and cigarette smoking.

3. The method of claim 1, wherein said compound is in the form of a salt.

4. A method according to claim 1, wherein said composition is formulated as a solution, gel, lotion, cream, or ointment.

5. The method according to claim 1, wherein the period of time is at least three months.

6. The method according to claim 1, wherein the period of time is at least four months.

7. The method according to claim 1, wherein said topical application is on a daily basis.

8. The method according to claim 1, wherein said skin changes associated with aging result from natural or innate aging.

9. The method according to claim 1, wherein said skin changes associated with aging result from exposure to actinic radiation.

10. The method according to claim 1, wherein said compound is the principal ingredient responsible for effecting said skin change.

11. The method according to claim 1, wherein said method results in skin having a more youthful appearance.

12. The method according to any of claims 1-11, wherein said compound is glycolic acid or a topically effective salt thereof.

13. The method according to any of claims 1-11, wherein said compound is lactic acid in D, L or DL form, or a topically effective salt thereof.

14. The method according to any of claims 1-11, wherein said compound is citric acid or a topically effective salt thereof.

* * * * *

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REEXAMINATION CERTIFICATE (3277th)

United States Patent [19] **B1 5,547,988**

Yu et al. [45] Certificate Issued **Jul. 15, 1997**

[54] **ALLEVIATING SIGNS OF
Dermatological Aging With
Glycolic Acid, Lactic Acid or Citric
Acid**

[75] Inventors: **Ruey J. Yu, Ambler; Eugene J. Van
Scott, Abington, both of Pa.**

[73] Assignee: **Tristrata Technology, Inc.,
Wilmington, Del.**

Reexamination Request:
No. 90/004,435, Oct. 28, 1996

Reexamination Certificate for:

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Filed:	Dec. 20, 1994

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[63] Continuation of Ser. No. 117,559, Sep. 7, 1993, abandoned, which is a continuation of Ser. No. 936,863, Aug. 27, 1992, abandoned, which is a continuation of Ser. No. 683,437, Apr. 10, 1991, abandoned, which is a continuation-in-part of Ser. No. 469,738, Jan. 19, 1990, abandoned, which is a continuation of Ser. No. 945,680, Dec. 23, 1986, abandoned, and a continuation-in-part of Ser. No. 393,749, Aug. 15, 1989, Pat. No. 5,091,171.

[51] **Int. Cl.⁶** A61K 7/48; A61K 31/19

[52] **U.S. Cl.** 514/557; 514/574; 514/844;
514/847; 514/873

[58] **Field of Search** 514/557, 574,
514/844, 847, 873

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Primary Examiner—James J. Seidleck

[57] **ABSTRACT**

Uses of topical compositions comprising a 2-hydroxycarboxylic acid or related compound to alleviate or improve signs of skin, nail and hair changes associated with intrinsic or extrinsic aging are disclosed. 2-Hydroxycarboxylic acids and their related compounds include, for example, 2-hydroxyethanoic acid, 2-hydroxypropanoic acid 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid, 2-phenyl 3-hydroxypropanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-hydroxybutane-1,4-dioic acid, 2,3-hydroxybutane-1,4-dioic acid, 2-carboxy 2-hydroxypentane-1,5-dioic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate, ethyl 2-ketopropanoate, and gluconolactone. Topical application of compositions comprising 2-hydroxycarboxylic acid and/or related compounds has been found to alleviate or improve skin lines; blotches; blemishes; nodules; wrinkles; pigmented spots; atrophy; precancerous lesions; elastotic changes characterized by leathery, coarse, rough, dry and yellowish skin; and other skin changes associated with intrinsic aging or skin damages caused by extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke and cigarette smoking. Topical applications of such compositions have also been found to improve the overall qualities of nail and hair affected by intrinsic aging or damaged by extrinsic factors.

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**REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307**

NO AMENDMENTS HAVE BEEN MADE TO
THE PATENT

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AS A RESULT OF REEXAMINATION, IT HAS BEEN
DETERMINED THAT:

The patentability of claims 1-14 is confirmed.

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EXHIBIT B



US005422370A

United States Patent [19]

Yu et al.

[11] Patent Number: **5,422,370**

[45] Date of Patent: * Jun. 6, 1995

[54] **METHOD OF USING
2-HYDROXYPROPANOIC ACID (LACTIC
ACID) FOR THE TREATMENT OF
WRINKLES**

[76] Inventors: **Ruey J. Yu, 4 Lindenwold Ave.,
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19001**

[*] Notice: The portion of the term of this patent
subsequent to Feb. 25, 2009 has been
disclaimed.

[21] Appl. No.: **179,189**

[22] Filed: **Jan. 10, 1994**

Related U.S. Application Data

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a division of Ser. No. 8,223, Jan. 22, 1993, which is a
continuation of Ser. No. 812,858, Dec. 23, 1991, aban-
doned, which is a continuation of Ser. No. 469,738,
Jan. 19, 1990, abandoned, which is a continuation of
Ser. No. 945,680, Dec. 23, 1986, abandoned.

[51] Int. Cl.⁶ **A61K 7/48; A61K 31/19**

[52] U.S. Cl. **514/557; 514/844**

[58] Field of Search **514/557, 844**

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Primary Examiner—Mukund J. Shah

Assistant Examiner—Philip I. Datlow

Attorney, Agent, or Firm—Foley & Lardner

[57] ABSTRACT

A method for visibly reducing a skin wrinkle by topically applying to the wrinkle lactic acid or a topically effective salt thereof.

11 Claims, No Drawings

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**METHOD OF USING 2-HYDROXYPROPANOIC
ACID (LACTIC ACID) FOR THE TREATMENT OF
WRINKLES**

This application is a continuation of application Ser. No. 08/089,101, now allowed, filed Jul. 12, 1993, which is a divisional of U.S. application Ser. No. 08/008,223, filed Jan. 22, 1993, pending which is a continuation of U.S. application Ser. No. 07/812,858, filed on Dec. 23, 1991, now abandoned, which is a continuation of U.S. application Ser. No. 07/469,738, filed on Jan. 19, 1990, now abandoned, which is a continuation of U.S. application Ser. No. 06/945,680, filed on Dec. 23, 1986, now abandoned.

This invention relates generally to method and composition containing hydroxyacid or related compound for enhancing therapeutic effects of cosmetic or pharmaceutical agent. As will be subsequently described in detail, we initially discovered that alpha hydroxy or keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne and warts.

We have now discovered that hydroxyacids or related compounds wherein incorporated into a therapeutic composition can substantially enhance topical effects of cosmetic and pharmaceutical agents.

In our prior U.S. Pat. No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoes" we described and claimed the use of certain alpha hydroxy acids, alpha keto acids and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans. In our U.S. Pat. No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of these certain alpha hydroxy acids, alpha keto acids and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

In our prior U.S. Pat. No. 4,105,783 entitled "Treatment of Dry Skin" we described and claimed the use of alpha hydroxy acids, alpha keto acids and their derivatives for topical treatment of dry skin. In our recent U.S. Pat. No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxy acids, alpha keto acids and their derivatives, in small amounts could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

In our more recent U.S. Pat. No. 4,363,815 entitled "Alpha Hydroxy acids, Alpha Keto acids and Their Use in Treating Skin Conditions" we described and claimed that alpha hydroxy acids and alpha keto acids related to or originating from amino acids, whether or not found in proteins, were effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus and possibly warts and herpes.

In our most recent U.S. Pat. No. 4,518,789 entitled "Phenyl Alpha-Acyloxyacetamide Derivatives and Their Therapeutic Use" we described and claimed that phenyl alpha acyloxyacetamide derivatives in topical or systemic administration were useful and effective for pruritus, atopic dermatitis, eczema, psoriasis, acne, dry skin, dandruff, malodors of integumental areas, various

aches, pains and discomforts of skin, joints and other body parts in humans and domestic animals.

The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by systemic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors a) Percutaneous absorption and penetration b) Bioavailability of the penetrated pharmaceutical agent to the target site in the skin. To be therapeutically effective as a topical agent a pharmaceutical drug must penetrate the stratum corneum into the epidermal layers, distributed and bioavailable to the target sites for pharmacologic action. Many pharmacologic agents can readily penetrate the skin but they are not bioavailable to the target sites in the skin, therefore therapeutic effect is minimal and ineffective.

It has now been discovered that hydroxyacids and related compounds including those described or not described in our previous patents and additional compounds can substantially enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders or other afflictions. Cosmetic and pharmaceutical agents may include any chemical substances natural or synthetic, intended for topical application to the skin or its appendages in human and animals. Some examples of cosmetic and pharmaceutical agents include age spots and keratoses removing agents, analgesics, anesthetics, antiacne agents, antibacterials, antiyeast agents, antifungal agents, antiviral agents, antiburn agents, antidandruff agents, antidermatitis agents, antipruritic agents, antiperspirants, antiinflammatory agents, antihyperkeratolytic agents, antidryskin agents, antipsoriatric agents, antiseborrheic agents, astringents, softeners, emollient agents, coal tar, bath oils, sulfur, rinse conditioners, foot care agents, fungicides, hair growth promoters, hair removers, keratolytic agents, moisturizer agents, powder, shampoos, skin bleaches, skin protectants, soaps, cleansers, antiaging agents, sunscreen agents, wart removers, wet dressings, vitamins, tanning agents, topical antihistamin agents, hormones, vasodilators, retinoids, bronchial dilators, topical cardiovascular agents and other dermatologicals.

The enhancing compounds of the instant invention are hydroxycarboxylic acids and related compounds. There are three groups of such hydroxyacids. The first is hydroxymonocarboxylic acids having the following chemical structure:



wherein

R₁, R₂=H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms.

m=1, 2, 3, 4, 5, 6, 7, 8 or 9

n=0 or a numerical number up to 23

When n=0 and m=1 or more, the hydroxymonocarboxylic acid is also called aldonic acid. The name comes from a carbohydrate, aldose, which may be oxidized to aldonic acid by the oxidation of the aldehyde group in aldose to the carboxylic group.

The hydroxymonocarboxylic acid may be present as a free acid, lactone, or salt form. The lactone form could be either inter or intramolecular lactone, how-

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ever, most common ones are intramolecular lactones with a ring structure formed by elimination of one or more water molecules between a hydroxy group and the carboxylic group. Since the hydroxymonocarboxylic acids are organic in nature, they may form a salt or a complex with an inorganic or organic base such as ammonium hydroxide, sodium or potassium hydroxide, or triethanolamine.

The hydroxymonocarboxylic acid and its related compounds may also exist as stereoisomers such as D, L, and DL forms.

The typical alkyl, aralkyl and aryl groups for R₁ and R₂ hydrogen atoms of the R₁ and R₂ and (CH₂)_n may be substituted by include methyl, ethyl, propyl, isopropyl, benzyl and phenyl. The a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy, saturated or unsaturated, having 1 to 9 carbon atoms. Representative hydroxymonocarboxylic acids are listed below:

1. 2-Hydroxyacetic acid (Glycolic acid)

R₁=H, R₂=H, m=1, n=0

2. 2-Hydroxypropanoic acid (Lactic acid)

R₁=CH₃, R₂=H, m=1, n=0

3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid)

R₁=CH₃, R₂=CH₃, m=1, n=0

4. 2-Hydroxybutanoic acid

R₁=C₂H₅, R₂=H, m=1, n=0

5. Phenyl 2-hydroxyacetic acid (Mandelic acid)

R₁=C₆H₅, R₂=H, m=1, n=0

6. Phenyl 2-methyl 2-hydroxyacetic acid (Atrolactic acid)

R₁=C₆H₅, R₂=CH₃, m=1, n=0

7. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid)

R₁=C₆H₅, R₂=H, m=1, n=1

8. 2,3-Dihydroxypropanoic acid (Glyceric acid)

R₁=H, R₂=H, m=2, n=0

9. 2, 3, 4-Trihydroxybutanoic acid

R₁=H, R₂=H, m=3, n=0

10. 2, 3, 4, 5-Tetrahydroxypentanoic acid

R₁=H, R₂=H, m=4, n=0

11. 2, 3, 4, 5, 6-Pentahydroxyhexanoic acid

R₁=H, R₂=H, m=5, n=0

12. 2-Hydroxydodecanoic acid (alpha hydroxylauric acid)

R₁=C₁₀H₂₁, R₂=H, m=1, n=0

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13. 2, 3, 4, 5, 6, 7-Hexahydroxyheptanoic acid

R₁=H, R₂=H, m=6, n=0

14. Diphenyl 2-hydroxyacetic acid (benzilic acid)

R₁=C₆H₅, R₂=C₆H₅, m=1, n=0

15. 4-Hydroxymandelic acid

R₁=C₆H₄(OH), R₂=H, m=1, n=0

16. 4-Chloromandelic acid

R₁=C₆H₄(Cl), R₂=H, m=1, n=0

17. 3-Hydroxybutanoic acid

R₁=CH₃, R₂=H, m=1, n=1

18. 4-Hydroxybutanoic acid

R₁=H, R₂=H, m=a, n=2

19. 2-Hydroxyhexanoic acid

R₁=C₄H₉, R₂=H, m=1, n=0

20. 5-Hydroxydodecanoic acid

R₁=C₇H₁₅, R₂=H, m=1, n=3

21. 12-Hydroxydodecanoic acid

R₁=H, R₂=H, m=1, n=10

22. 10-Hydroxydecanoic acid

R₁=H, R₂=H, m=1, n=8

23. 16-Hydroxyhexadecanoic acid

R₁=H, R₂=H, m=1, n=14

24. 2-Hydroxy-3-methylbutanoic acid

R₁=C₃H₇, R₂=H, m=1, n=0

25. 2-Hydroxy-4-methylpentanoic acid

R₁=C₄H₉, R₂=H, m=1, n=0

26. 3-Hydroxy-4-methoxymandelic acid

R₁=C₆H₃(OH)(OCH₃), R₂=H, m=1, n=0

27. 4-Hydroxy-3-methoxymandelic acid

R₁=C₆H₃(OH)(OCH₃), R₂=H, m=1, n=0

28. 2-Hydroxy-2-methylbutanoic acid

R₁=C₂H₅, R₂=CH₃, m=1, n=0

29. 3-(2-Hydroxyphenyl) lactic acid

R₁=C₆H₄(OH)CH₂, R₂=H, m=1, n=0

30. 3- (4-Hydroxyphenyl) lactic acid

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5 $R_1 = C_6H_4(OH)CH_2, R_2 = H, m = 1, n = 0$

31. Hexahydromandelic acid

 $R_1 = C_6H_{11}, R_2 = H, m = 1, n = 0$

32. 3 -Hydroxy-3-methylpentanoic acid

 $R_1 = C_2H_5, R_2 = CH_3, m = 1, n = 1$

33. 4 -Hydroxydecanoic acid

 $R_1 = C_6H_{13}, R_2 = H, m = 1, n = 2$

34. 5-Hydroxydecanoic acid

 $R_1 = C_5H_{11}, R_2 = H, m = 1, n = 3$

35. Aleuritic acid

 $R_1 = C_6H_{12}(OH), R_2 = H, m = 2, n = 7$

The linear lactic acid polymer is an intermolecular lactone formed by elimination of one water molecule between the hydroxy group of one molecule of lactic acid and the carboxylic group of a second molecule of lactic acid. The common linear lactic acid polymer may contain 3 lactic acid units.

Ribonic acid is one of the stereoisomers of 2, 3, 4, 5-tetrahydroxypentanoic acid, and the corresponding lactone is ribonolactone. Gluconic acid, galactonic acid, gulonic acid and mannonic acid are typical 2, 3, 4, 5, 6-pentahydroxyhexanoic acids and their corresponding lactones are gluconolactone, galactonolactone, gulonolactone and mannonolactone respectively. The related compounds of hydroxymonocarboxylic acids are ketomonocarboxylic acids which are formed from the former by an oxidation reaction or in vivo by a dehydrogenase enzyme. For example, 2-ketopropanoic acid (pyruvic acid) and 2-hydroxypyropanoic acid (lactic acid) are converted to each other in vivo by the enzyme, lactate dehydrogenase. Although pure pyruvic acid (liquid form) can be kept in a refrigerator for an extended period of time a composition containing pyruvic acid for topical use is not very stable at an elevated temperature. Therefore, for practical purposes pyruvic acid esters are used instead.

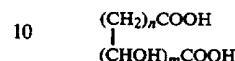
The representative esters are methyl pyruvate, ethyl pyruvate, propyl pyruvate and isopropyl pyruvate. Other representative ketomonocarboxylic acids and their esters are phenyl pyruvic acid and its esters such as methyl phenyl pyruvate, ethyl phenyl pyruvate and propyl phenyl pyruvate; formyl formic acid (2-ketoacetic acid) and its esters such as methyl, ethyl and propyl formyl formate; benzoyl formic acid and its esters such as methyl, ethyl and propyl benzoyl formate; 4-hydroxybenzoylformic acid and its esters; 4-hydroxyphenylpyruvic acid and its esters; 2-hydroxyphenylpyruvic acid and its esters.

Many hydroxy or ketomonocarboxylic acids are structurally related to amino acids either naturally occurring in proteins or not. For example alanine and pyruvic acid are interconverted to each other in vivo by an enzyme alanine dehydrogenase or alanine ketoglutarate transaminase. As mentioned earlier pyruvic acid and lactic acid are interconverted to each other in vivo by the enzyme lactate dehydrogenase. Therefore, alanine, pyruvic acid and lactic acid are chemically related in that the amino group of alanine may be converted to the keto group of pyruvic acid or the hydroxy group of

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lactic acid. The same relationships may apply to formyl formic acid and glycolic acid to glycine; hydroxypyruvic acid and glyceric acid to serine; phenyl pyruvic acid and phenyl lactic acid to phenylalanine; 2-keto- and 2-hydroxy-4 (methylthio) butanoic acids to methionine.

The second kind of hydroxyacid is hydroxydicarboxylic acid having the following chemical structure:



wherein

 $m = 1, 2, 3, 4, 5, 6, 7, 8$ or 9 15 $n = 0$ or a numerical number up to 23

The hydroxydicarboxylic acid may also be present as a free acid, lactone or salt form. The lactone form could be either inter or intramolecular lactone. However, the common lactone is an intramolecular lactone with a

20 ring structure formed by elimination of one or more water molecule between a hydroxy group and one of the carboxylic groups. Since the hydroxydicarboxylic acid is organic in nature, it may form a salt or a complex with an inorganic or organic base such as ammonium

25 hydroxide, sodium or potassium hydroxide, or triethanolamine.

The hydroxydicarboxylic acid and its related compounds may also exist as stereoisomers such as D, L, DL and meso forms.

30 The hydrogen atom attached to the carbon atom may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy of saturated or unsaturated, having 1 to 9 carbon atoms.

When $n = 0$ and $m = 1$ or more, the hydroxydicarboxylic acid is also called aldaric acid. The name comes from the carbohydrate, and the common ones are saccharic acid and galactaric acid. Representative hydroxydicarboxylic acids are listed below:

40 1. 2-Hydroxypropanedioic acid (Tartronic acid)

 $m = 1, n = 0$

2. 2-Hydroxybutanedioic acid (Malic acid)

45 $m = 1, n = 1$

3. Erythraric acid and Threanic acid (Tartaric acid)

50 $m = 2, n = 0$

4. Arabiraric acid, Ribaric acid, Xylaric acid and Lyxaric acid

55 $m = 3, n = 0$

5. Glucaric acid (saccharic acid), Galactaric acid (Mucic acid), Mannaric acid, Gularic acid, Allaric acid, Altraric acid, Idaric acid and Talaric acid

60 $m = 4, n = 0$

Commercially available saccharolactone (D-saccharic acid 1, 4-lactone) is an intramolecular lactone formed by elimination of one water molecule between the hydroxy group at position 4 and the carboxylic group at position 1.

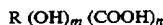
65 The third type of hydroxyacid is a miscellaneous group of compounds which is not readily represented

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by the above generic structure of either the first type or the second type. Included in the third type of hydroxyacids are the following:

Hydroxycarboxylic acid of



Wherein m,n=1,2,3,4,5,6,7,8, or 9

R=H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having 1 to 25 carbon atoms.

citric acid, isocitric acid, citramalic acid, agaricic acid (n-hexadecylcitric acid), quinic acid, uronic acids including glucuronic acid, glucuronolactone, galactouronic acid, galacturonolactone, hydroxypyruvic acid, hydroxypyruvic acid phosphate, ascorbic acid, dihydroascorbic acid, dihydroxytartaric acid, 2-hydroxy-2-methylbutanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 2-hydroxyhexanedial, 5-hydroxylysine, 3-hydroxy-2-aminopentanoic acid, tropic acid, 4-hydroxy-2-, 2-diphenylbutanoic acid, 3-hydroxy-3-methylglutaric acid, and 4-hydroxy-3-pentenoic acid.

The third type of hydroxyacid may also be present as a free acid, lactone or salt form. The lactone form could be either an inter or intramolecular lactone, however, most common are intramolecular lactones with a ring structure. Commonly known glucuronolactone is a r-lactone i.e. 1,4-lactone of intramolecular type.

The hydroxyacid of the third type may also exist as stereoisomers such as D, L, DL and meso forms. The hydrogen atom attached to the carbon atom may be substituted by a nonfunctional element such as F, Cl, Br, I, S or a radical such as a lower alkyl or alkoxy of saturated or unsaturated, having 1 to 9 carbon atoms.

Any hydroxyacid and related compound of the above three kinds may be used as an additive in a combination composition to enhance the percutaneous penetration or the therapeutic efficacy of cosmetic and pharmaceutical agents. The cosmetic and pharmaceutical agents may include but not limited to: age spots and keratoses removing agents, vitamins, aloes, retinoids, sun screens; tanning, depigmenting and shampooing agents; antiperspirants, antiyeasts, antifungal, antibacterial and antiviral agents; topical bronchial dilators; topical cardiovascular agents; keratoses, age spots and wrinkles removal agents, hair growth promoting agents and other dermatological agents.

Hydroxyacids and related compounds may also be used alone in the prophylactic and therapeutic treatment of cosmetic conditions or dermatologic disorders characterized by disturbed keratinization, aging, lipid metabolism or inflammation. The representative hydroxyacids are listed below:

citramalic acid, tropic acid, benzilic acid, ribonic acid and ribonolactone, gulonic acid and gulonolactone, 2,3,4-trihydroxybutanoic acid, 2,3,4,5-tetrahydroxypentanoic acid, 2,3,4,5,6-pentahydroxyhexanoic acid, 2-hydroxyalauric acid, 2,3,4,5,6,7-hexahydroxyheptanoic acid, aleuritic acid, 4-hydroxymandelic acid, 4-chloromandelic acid, 2-hydroxy-3-methylbutanoic acid, 2-hydroxy-4-methylpentanoic acid, 3-hydroxy-3-methylbutanoic acid, 2-hydroxy-4-methylpentanoic acid, 3-hydroxy-4-methoxymandelic acid, 4-hydroxy-3-methoxymandelic acid, 3-(2-hydroxyphenyl) lactic acid, 3-(4-hydroxyphenyl) lactic acid, hexahydromandelic acid, 3-hydroxy-3-methylpentanoic acid, 1-hydroxy-1-cyclopropane carboxylic acid, 4-hydroxybutanoic acid, 2-hydroxyhexanoic acid, 5-hydroxylauric acid, 12-hydroxylauric acid, 10-hydroxydecanoic

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acid, 16-hydroxyhexadecanoic acid, 4hydroxydecanoic acid, 5-hydroxydecanoic acid, and 4-hydroxy-2, 2-diphenylbutanoic acid.

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Preparation of the Therapeutic Compositions

To prepare a therapeutic composition in solution form at least one of the aforementioned enhancing compounds of hydroxyacids and a cosmetic or pharmaceutical agent are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicles. The concentration of hydroxyacids may range from 0.01 to 99 percent by weight of the total composition. The concentration of the cosmetic or pharmaceutical agent ranges from 0.01 to 40 percent by weight of the total composition.

In the preparation of a therapeutic composition in cream or ointment form at least one of hydroxyacids and one of cosmetic or pharmaceutical agents are initially dissolved in a solvent such as water, ethanol, acetone, propylene glycol or polysorbate 80. the solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of hydroxyacids, cosmetic and pharmaceutical agents may range from 0.01 to 99 percent by weight of the total composition.

Therapeutic compositions of the instant invention may also be formulated in gel, lotion, shampoo, spray, stick or powder. A typical gel composition of the instant invention utilizes at least one of hydroxyacids and one of cosmetic or pharmaceutical agents dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limitative. Therefore, any of the aforementioned hydroxyacids, cosmetic and pharmaceutical agents may be substituted according to the teachings of this invention in the following examples.

Example 1

A prophylactic and therapeutic composition in solution form for age spots and for keratoses may be prepared as follows.

Malic acid 1 gram, gluconolactone 19 grams and citric acid 0.5 gram are dissolved in a mixture of ethanol 30 ml, water 42 ml and glycerin 5 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The hydroxyacids, malic acid, gluconolactone and citric acid have been added a) as antioxidants to help stabilize the hydroquinone in the composition b) to enhance the penetration and the efficacy of hydroquinone c) to normalize the disturbed keratinization in age spot and keratoses.

The composition thus formulated contains 2% hydroquinone, 1% malic acid, 19% gluconolactone, 0.5% citric acid, and has pH 3.3

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Example 2

A therapeutic composition in solution form for age spots and for keratoses may be formulated as follows.

Alpha hydroxyisobutyric acid (Methylallic acid) 20 grams and citric acid 2 grams are dissolved in a mixture of ethanol 49 ml, water 20 ml and propylene glycol 7 ml. Sodium bisulfite 0.5 g and hydroquinone 2 grams are added with stirring until a clear solution is obtained. The composition thus formulated contains hydroquinone, 2% citric acid, 20% methylallic acid, and has pH 3.6.

Example 3

A prophylactic and therapeutic composition containing minoxidil and lactic acid for hair growth and for prevention of hair loss on the scalp may be formulated as follows.

Minoxidil 2 grams and lactic acid 3 ml are dissolved in a mixture of ethanol 80 ml and propylene glycol 15 ml with stirring until a clear solution is obtained. The composition thus formulated contains 2% minoxidil, 3% lactic acid, and has pH 4.7. The lactic acid has been added to help minoxidil dissolved into solution, to enhance the penetration and the efficacy of minoxidil for hair growth.

Example 4

A prophylactic and therapeutic composition in solution form for hair growth on the scalp may be formulated as follows.

Minoxidil 2 grams and ethyl pyruvate 2 ml are dissolved in a mixture of ethanol 80 ml and propylene glycol 16 ml. The composition thus formulated contains 2% minoxidil, 2% ethyl pyruvate, and has pH 5.0. The ketoacid ester, ethyl pyruvate has been added to enhance the penetration and the efficacy of minoxidil for hair growth on the scalp.

Example 5

A therapeutic composition containing anthralin and hydroxyacid for psoriasis may be formulated as follows.

Anthralin powder 0.5 gram and alpha hydroxyisobutyric acid 4 grams are dissolved in a mixture of ethanol 50 ml, acetone 30 ml and diisopropyl adipate 16 ml with stirring until a clear yellowish solution is obtained. The composition thus formulated contains 0.5% anthralin, 4% alpha hydroxyisobutyric acid, and has pH 4.2. The hydroxyacid has been added to enhance the penetration and the efficacy of anthralin for psoriasis.

Example 6

A therapeutic composition containing thionicotinamide and hydroxyacid for psoriasis, keratoses and warts may be formulated as follows.

Thionicotinamide 2 grams and lactic acid 20 ml are dissolved in a mixture of ethanol 40 ml, water 30 ml and propylene glycol 8 ml with stirring until a clear yellowish solution is obtained. The composition thus formulated contains 2% thionicotinamide, 20% lactic acid, and has pH 3.3. The lactic acid has been added to enhance the penetration and the efficacy of thionicotinamide, and also to normalize the disturbed keratinization in psoriasis, keratoses and warts.

A therapeutic composition containing 6-aminonicotinamide and hydroxyacid for psoriasis, keratoses and warts may be formulated as follows.

6-Aminonicotinamide 1 gram and glycolic acid 19 grams are dissolved in a mixture of ethanol 40 ml, water 32 ml and propylene glycol 8 ml with stirring until a clear solution is obtained. The composition thus formulated contains 1% 6-aminonicotinamide, 19% glycolic acid, and has pH 3.0. The glycolic acid has been added to enhance the penetration and the efficacy of 6-Aminonicotinamide, and also to normalize the disturbed keratinization in psoriasis, keratoses and warts.

Example 8

A therapeutic composition containing clotrimazole and hydroxyacid for fungal infection may be formulated as follows.

Clotrimazole 1 gram and lactic acid 4 ml are dissolved in 4 ml of ethanol, and the solution thus obtained is mixed with 91 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 1% clotrimazole, 4% lactic acid, and has pH 3.2. The lactic acid has been added to enhance the penetration and the efficacy of clotrimazole for athlete's foot, and also to speed up healing and normalize the disturbed keratinization.

Example 9

A prophylactic and therapeutic composition containing chlorhexidine and hydroxyacid as general antiseptics on skin, and for prophylactic and therapeutic treatment of acne may be formulated as follows. Chlorhexidine diacetate 1 gram and benzilic acid 5 grams are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 14 ml with stirring until a clear solution is obtained. The composition thus formulated contains 1% chlorhexidine, 5% benzilic acid, and has pH 4.4. Benzilic acid has been added to enhance the antibacterial effect of chlorhexidine, to eliminate the oiliness of the skin, and to improve the acne lesions.

Example 10

A prophylactic and therapeutic composition containing benzilic acid as the only active ingredient for oily skin, acne, skin cleansing and skin malodor may be formulated as follows.

Benzilic acid 7 grams is dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 13 ml with stirring until a clear solution is obtained. The composition thus prepared contains 7% benzilic acid, and has pH 3.0.

Example 11

A therapeutic composition containing tropic acid as the only active ingredient for severe dry skin may be formulated as follows.

Tropic acid 10 grams is dissolved in 20 ml of ethanol, and the solution thus obtained is mixed with 70 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 10% tropic acid as an active ingredient, and has pH 3.7.

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11**Example 12**

A prophylactic and therapeutic composition containing ribonolactone as the only active ingredient for oily skin, acne and skin cleansing may be formulated as follows.

Ribonolactone 4 grams is dissolved in a mixture of ethanol 36 ml and water 60 ml with stirring until a clear solution is obtained. The composition thus prepared contains 4% ribonolactone as an active ingredient, and has pH 3.8.

Example 13

A therapeutic composition containing hydrocortisone and tropic acid for inflammatory and/or pruritic skin disorders may be formulated as follows.

Hydrocortisone 0.5 gram and tropic acid 5 grams are dissolved in 10 ml of ethanol and 4 ml of acetone, and the solution thus obtained is mixed with 80 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 0.5% hydrocortisone and 5% tropic acid as active ingredients, and has pH 3.4. The tropic acid has been added to enhance the penetration and the efficacy of hydrocortisone and also to normalize the disturbed keratinization.

Example 14

A therapeutic composition containing triamcinolone acetonide and benzilic acid for eczema, psoriasis and other inflammatory and pruritic skin disorders may be formulated as follows.

Triamcinolone acetonide 0.1 gram and benzilic acid 5 grams are dissolved in 10 ml of ethanol, and the solution thus obtained is mixed with 85 grams of hydrophilic ointment USP. The mixing is continued until a uniform consistency is obtained. The composition thus formulated contains 0.1% triamcinolone acetonide, 5% benzilic acid, and has pH 3.4. The benzilic acid has been added to enhance the penetration and the efficacy of triamcinolone acetonide, and also to normalize the disturbed keratinization in eczema, psoriasis and other inflammatory skin disorders.

Example 15

A prophylactic and therapeutic composition containing dipyridamole and lactic acid for hair growth and for prevention of hair loss on the scalp may be formulated as follows.

Dipyridamole 2 grams and lactic acid 4 ml are dissolved in a mixture of ethanol 80 ml and propylene glycol 14 ml with stirring until a clear yellowish solution is obtained. The composition thus formulated contains 2% dipyridamole, 4% lactic acid, and has pH 4.4. The lactic acid has been added to help dipyridamole dissolved into solution, to enhance the penetration and the efficacy of dipyridamole for hair growth and for preventing hair loss.

Example 16

A therapeutic composition containing clobetasol propionate and agaricic acid for eczema, psoriasis and other inflammatory and pruritic skin disorders may be formulated as follows.

Agaricic acid fine powder 2 grams and 98 grams of clobetasol propionate cream are mixed until a uniform consistency is obtained. The composition thus formulated contains approximately 0.05% clobetasol propio-

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nate, 2% agaricic acid, and has pH 4.3. The agaricic acid has been added to enhance the penetration and the efficacy of clobetasol propionate, and also to normalize the disturbed keratinization in eczema, psoriasis and other inflammatory skin disorders.

Example 17

A therapeutic composition containing betamethasone dipropionate and benzilic acid for eczema, psoriasis, contact dermatitis and other inflammatory and pruritic skin disorders may be formulated as follows.

Benzilic acid powder 5 grams and 95 grams of betamethasone dipropionate ointment are mixed until a uniform consistency is obtained. The composition thus formulated contains approximately 0.05% betamethasone dipropionate and 5% benzilic acid. The benzilic acid has been added to enhance the penetration and the efficacy of betamethasone dipropionate, and also to normalize the disturbed keratinization in eczema, psoriasis and other inflammatory skin disorders.

Example 18

A prophylactic and therapeutic composition containing aloe, malic acid and gluconolactone for oily skin and acne may be formulated as follows.

Aloe powder 200 fold 0.2 gram and ammoniated glycyrrhizinate 2 grams are mixed with water 61 ml and propylene glycol 2 ml. The mixture is heated to 50° C. until the aloe powder and the ammoniated glycyrrhizinate are completely dissolved. Ethanol 10 ml is added to the solution followed by the addition of partially neutralized malic acid stock solution 3 ml and gluconolactone stock solution 22 ml with stirring. The warm solution is poured into container jars before cooling. The gel composition thus formulated contains 40% aloe, 1% malic acid, 9% gluconolactone, and has pH 4.0. Malic acid and gluconolactone have been added to enhance the skin softness and smoothness by aloe, and also to normalize any disturbed keratinization of the skin.

Example 19

A sun screen composition containing Octyl dimethyl PABA, dioxybenzone and lactic acid may be formulated as follows. Octyl dimethyl PABA 5 grams, dioxybenzone 3 grams and lactic acid 2 ml are dissolved in a mixture of ethanol 65 ml, water 10 ml and propylene glycol 15 ml with stirring until a clear solution is obtained. The composition thus formulated contains 5% octyl dimethyl PABA, 3% dioxybenzone, 2% lactic acid, and has pH 3.6. The lactic acid has been added to substantiate the absorption of sunscreen agents, octyl dimethyl PABA and dioxybenzone, and to enhance the sun screen effect.

Example 20

A prophylactic and therapeutic composition containing tetracycline and glycolic acid for oily skin and acne may be formulated as follows.

Tetracycline 3 grams and glycolic acid 5 grams are dissolved in a mixture of ethanol 40 ml, water 40 ml and propylene glycol 12 ml with stirring until the tetracycline and glycolic acid are completely dissolved. The composition thus formulated contains 3% tetracycline, 5% glycolic acid, and has pH 3.4. The glycolic acid has been added to help tetracycline dissolved into the solution, to enhance the penetration and the efficacy of tetracycline, and to normalize the disturbed keratinization in acne.

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13**Example 21**

A therapeutic composition containing griseofulvin and methyl pyruvate for fungal infection of nails may be formulated as follows.

Griseofulvin 1 gram and methyl pyruvate 2 ml are dissolved in a mixture of 2-pyrrolidone 20 ml, PEG-400 47 ml and ethanol 30 ml with stirring until the griseofulvin is completely dissolved. The composition thus formulated contains 1% griseofulvin, 2% methyl pyruvate, and has pH 4.4. The methyl pyruvate has been added to help griseofulvin dissolve into the solution, to enhance the penetration and the efficacy of griseofulvin, and to normalize the disturbed keratinization in nails.

Example 22

A therapeutic composition containing lidocaine and atrolactic acid for pruritic skin may be formulated as follows.

Lidocaine 2 grams and atrolactic acid hemihydrate 3 grams are dissolved in a mixture of ethanol 40 ml, water 40 ml and propylene glycol 15 ml with stirring until the lidocaine and atrolactic acid are completely dissolved. The composition thus formulated contains 2% lidocaine, 3% atrolactic acid, and has pH 4.6. The atrolactic acid has been added to help lidocaine dissolved and stabilized in the solution and to enhance the efficacy of lidocaine for pruritic skin.

Example 23

A prophylactic and therapeutic composition containing retinoic acid and ethyl pyruvate for oily skin and acne may be formulated as follows.

Retinoic acid, all-trans 0.1 gram and ethyl pyruvate 2 ml are dissolved in a mixture of ethanol 80 ml, water 10 ml and propylene glycol 8 ml with stirring until a yellowish solution is obtained. The composition thus formulated contains 0.1% vitamin A acid, 2% ethyl pyruvate, and has pH 3.6. The ethyl pyruvate has been added to enhance the penetration and the efficacy of retinoic acid, and to normalize the disturbed keratinization in acne.

Example 24

A prophylactic and therapeutic composition containing erythromycin and aleuritic acid for oily skin and acne may be formulated as follows.

Erythromycin 2 grams and aleuritic acid 2 grams are dissolved in a mixture of ethanol 50 ml, water 40 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The composition thus formulated contains 2% erythromycin, 2% aleuritic acid, and has pH 5.7. The aleuritic acid has been added to help erythromycin dissolve into the solution, to enhance the penetration and the efficacy of erythromycin, and to normalize the disturbed keratinization in acne.

Example 25

A therapeutic composition containing P-hydroxy-mandelic acid for dry skin may be formulated as follows.

P-Hydroxymandelic acid 10 grams is dissolved in 20 ml of ethanol, and the pinkish solution thus obtained is mixed with 70 grams of hydrophilic ointment USP with stirring until a uniform consistency is obtained. The composition thus formulated contains 10% P-hydroxymandelic acid as an active ingredient, and has pH 3.2. P-Hydroxymandelic acid has been incorporated into

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the composition to alleviate any scaly or flaky skin, and to change the dry skin into normal smooth and soft skin.

Example 26

5 A therapeutic composition containing hydroquinone and lactic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

Lactic acid 10 ml, hydroquinone 4 grams and sodium metabisulfite 0.6 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 6 ml with stirring until a clear solution is obtained. The composition thus formulated contains 4% hydroquinone, 10% lactic acid, and has pH 4.0. The lactic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus formulated is packaged in felt pens for controlled delivery to skin lesions.

Example 27

A therapeutic composition containing hydroquinone and glycolic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

Glycolic acid 8 grams, hydroquinone 5 grams and sodium metabisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 10 ml and propylene glycol 7 ml with stirring until a clear solution is obtained. The composition thus formulated contains 5% hydroquinone, 8% glycolic acid, and has pH 3.9. The glycolic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions. The composition thus prepared is packaged in felt pens for controlled delivery to skin lesions.

Example 28

A therapeutic composition containing hydroquinone and 2-methyl 2-hydroxypropanoic acid in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows.

2-Methyl 2-hydroxypropanoic acid 12 grams, hydroquinone 4 grams and sodium bisulfite 0.3 gram are dissolved in a mixture of ethanol 60 ml, water 20 ml and propylene glycol 4 ml with stirring until a clear solution is obtained. The composition thus formulated contains 4% hydroquinone, 12% 2-methyl 2-hydroxypropanoic acid, and has pH 4.0. The composition solution is packaged in felt pens for controlled delivery to skin lesions. The 2-methyl 2-hydroxypropanoic acid has been added to help stabilize and enhance the penetration and the efficacy of hydroquinone, and also to normalize the disturbed keratinization in the skin lesions.

Example 29

A composition containing hydroquinone alone in solution form for age spots and keratoses studies may be formulated as follows.

Hydroquinone 5 grams and sodium metal bisulfite 0.5 gram are dissolved in a mixture of ethanol 70 ml, water 15 ml and propylene glycol 10 ml with stirring until a clear solution is obtained. The composition thus prepared contains 5% hydroquinone and has pH 6.0. The composition solution is packaged in felt pens for comparative studies; with or without hydroxyacids on age spots and keratoses.

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TEST RESULTS

In order to determine whether addition of a hydroxyacid in the composition could enhance the therapeutic action of a cosmetic or pharmaceutical agent a total of more than 55 volunteers and patients having different skin disorders participated in these studies. Each participating subject was given two preparations; i.e. with or without the addition of a hydroxyacid in the therapeutic composition.

Topical applications were carried out either by bilateral or sequential comparison. In bilateral comparison the subject was instructed to apply one preparation on one side of the body and the other one on the other side

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solvents, chemicals, etc., again caused recurrence of the dry skin condition. On continued use it was also found that twice daily topical application of a composition containing one or more hydroxyacids of instant invention prevented the development of new dry skin lesions.

- In severe dry skin the skin lesions are different from the above. The involved skin is hyperplastic, fissured and has thick adherent scales. The degree of thickening is such that lesions are palpably and visually elevated.
- 10 The thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. The two attributes of thickness and texture can be quantified to allow objective measurement of degree of improvement from topically applied therapeutic test materials as

DEGREE OF IMPROVEMENT					
	None (0)	Mild (1+)	Moderate (2+)	Substantial (3+)	Complete (4+)
THICKNESS	Highly elevated	Detectable reduction	Readily apparent reduction	Barely elevated	Normal thickness
TEXTURE	Visibly rough	Palpably rough	Uneven but not rough	Slightly uneven	Visibly and palpably smooth

of the body. For psoriasis, eczema, severe dry skin, athlete's foot, etc., where both sides were involved, the subject was instructed to apply two to three times daily one medication on one side of the body for a period of up to several months of time. In the pulse treatment for psoriasis or other inflammatory diseases the medication was applied only once every three days or twice a week. The medication was discontinued whenever a total remission of the lesions occurred prior to the test period of up to several months.

For the scalp or face involvement such as in dandruff, oily skin, acne and seborrheic dermatitis the subject was instructed to apply two to three time daily one medication on one side of the scalp or the face and the other medication on the other side of the scalp or the face for a period of up to 12 weeks of time. For age spots, keratoses or warts the medication was continued for up to 4 months of time.

Sequential administrations of medications were carried out whenever the bilateral comparison was difficult. For example, in pruritic conditions the subject was instructed to apply four time daily or as often as necessary one medication on the pruritic lesions for two days, then switched to the other medication on the same lesions for another two days, thus to compare which medication was more effective in relieving the itching.

1. Dry skin.

Human subjects having ordinary dry skin or with moderate degrees of dry skin as evidenced by dry, flaking and cracking of the skin were instructed to apply topically the lotion, cream or ointment containing 3 to 7 percent of hydroxyacids of the instant invention on the affected skin areas. Topical application, two to three times daily, was continued for two to three weeks. In all the nine subjects tested, the feeling of the skin dryness disappeared within a week of topical application. The rough and cracked skin became less pronounced and the skin appeared normal and felt smooth after 10 days of topical treatment.

The ordinary dry skin conditions once restored to normal appearing skin remained improved for some time until causes of dry skin, such as low humidity, cold weather, excessive contact pressure, detergents, soaps,

By means of such parameters degrees of change in lesions can be numerically noted and comparisons made of one treated site to another.

In order to evaluate the hydroxyacids and their related compounds of the instant invention a total of six patients with severe dry skin conditions or ichthyosis were treated with the compositions containing 7 to 15% of hydroxyacids as described in the Examples.

Treated areas were of a size convenient for topical applications, i.e., circles 5 cm in diameter demarcated with a plastic ring of that size inked on a stamp pad. The medicinal creams or ointments were topically applied by the patient in an amount sufficient to cover the treatment sites. Applications were made three time daily and without occlusive dressings. Applications were discontinued at any time when resolution of the lesion on the treatment area was clinically judged to be complete.

The test results on patients with severe dry skin are summarized on the following table.

Compounds	Topical Effectiveness of Hydroxyacids on Severe Dry Skin	
	Number of Patients	Therapeutic Effectiveness
1. Tropic acid	4	4+
2. Benziolic acid	5	4+
3. Ribonolactone	3	3+
4. 4-Hydroxymandelic acid	2	3+
5. 3-Chloro 4-hydroxymandelic acid	2	3+
6. 3,4-Dihydroxymandelic acid	2	3+

2. Psoriasis

The involved skin in psoriasis is hyperplastic (thickened), erythematous (red or inflamed), and has thick adherent scales. the degree of thickening is such that lesions are elevated up to 1 mm above the surface of adjacent normal skin; erythema is usually an intense red; the thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These three attributes of thickness, color and texture can be quantified to allow objective measurement of degree of improvement from topically applied therapeutic test materials as follows.

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	DEGREE OF IMPROVEMENT				
	None (0)	Mild (1+)	Moderate (2+)	Substantial (3+)	Complete (4+)
Thickness	Highly elevated	Detectable reduction	Readily apparent	Barely elevated	Normal thickness
Texture	Visibly rough	Palpably rough	Uneven but not rough	Slightly uneven	Visibly and palpably smooth
Color	Intense red	Red	Dark Pink	Light pink	Normal skin color

By means of such parameters degree of improvements in psoriatic lesions can be numerically recorded and comparisons made of one treated site to another. The treatment schedule was quite different from the previously described in that the present study was employing a "Pulse Treatment." Instead of several times daily application the therapeutic composition of antipsoriatic agent with or without a hydroxyacid in solution form was topically applied to the involved skin only once in every three days or twice a week. The test results on patients having psoriasis are summarized on the following table.

Topical Effects on Psoriasis of Antipsoriatic Agents With or without Hydroxyacids		
Compositions	Number of Patients	Therapeutic Effectiveness
Thionicotinamide 3% alone	6	2+
with 10% Lactic acid	6	4+
with 5% Glycolic acid	4	4+
with 5% 2-methyl 2-hydroxy-propanoic acid	3	4+
6-Aminonicotinamide 1% alone	5	3+
with 10% Lactic acid	5	4+
with 10% Glycolic acid	4	4+
Betamethasone dipropionate 0.05% ointment alone	5	3+
with 5% Benzilic acid	4	4+
with 5% Tropic acid	3	4+
with 5% 2-Methyl 2-Hydroxy-propanoic acid	3	4+
Clobetasol propionate 0.05% cream alone	4	2+
with 5% Benzilic acid	3	3+
with 5% Tropic acid	2	3+
with 5% 2-Methyl 2-hydroxy-propanoic acid	3	3+

In a topical treatment of eczema patients, betamethasone dipropionate or clobetasol propionate alone at 0.05% would achieve only a 3+ improvement on all the eczema patients tested. As shown by the table with the addition of 5% gluconolactone or ribonolactone betamethasone dipropionate or clobetasol propionate could attain a 4+ maximal clearing on all the eczema patients tested.

Topical Effects on Eczema of Corticosteroids With and Without Hydroxyacid Lactone		
Compositions	Number of Patients	Therapeutic Effectiveness
Betamethasone dipropionate 0.05% alone	3	3+
with 5% Gluconolactone	3	4+
with 5% Ribonolactone	2	4+
Clobetasol propionate 0.05% alone	4	3+
with 5% Gluconolactone	4	4+
with 5% Ribonolactone	3	4+

3. Age Spots, Wrinkles, Keratoses and Pigmented Skin lesions.

Therapeutic compositions packaged in felt pens as described in Examples were provided to 14 patients for treatment of age spots, wrinkles, keratoses and other pigmented skin spots. Each participating patient received two felt pens; i.e. with or without the addition of hydroxyacid to the composition containing hydroquinone. The patients were instructed to apply topically one medication on one side of the body such as on the back of the left hand and the other medication on the other side of the body such as on the back of the right hand. Specific instructions were given to the patients that the medications were applied twice daily and discretely only to the skin lesions of age spots, wrinkles, keratoses, melasmas, lentigines or other pigmented skin spots.

Within one to three weeks, improvement of age spots and keratoses was clinically discernible. After one to three months substantial eradication of age spots, wrinkles and keratoses occurred in all the patients tested. Complete eradication of age spots usually occurred within two to four months of topical administration in most cases. Therapeutic compositions containing higher concentrations of hydroxyacids (10 to 20%) and hydroquinone (3 to 5%) were judged to be more efficient in eradicating age spots, wrinkles and keratoses within shorter periods of time. Without the addition of a hydroxyacid to the composition of hydroquinone, eradication of age spots, wrinkles or keratoses did not occur within four months of time.

It was also found that while compositions containing hydroxyacids without hydroquinone were effective for eradication of keratoses and wrinkles, the compositions were not efficient in eradicating pigmented age spots, melasmas or lentigines within 4 months of time. In any case, with the addition of a hydroxyacid to the composition containing hydroquinone, pigmented age spots, melasmas, lentigines and other pigmented skin spots had been substantially eradicated.

4. Acne.

Therapeutic compositions containing tetracycline, erythromycin or chlorhexidine with or without the addition of a hydroxyacid were provided to 9 patients having papulopustular or pustular lesions of acne. Each participating patient received two medications, with or without the addition of a hydroxyacid to the composition containing an antibiotic. The patients were instructed to apply topically one medication on one side of the body such as the left side forehead, face, back or chest, and the other medication on the other side of the body such as right side forehead, face, back or chest. Twice daily administration was continued for 4 to 12 weeks.

The degree and rate of improvement on acne lesions were clinically evaluated, and comparison was made between the two sides; one side with and the other side

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without a hydroxyacid in the compositions containing an antibiotic. It was found that the degree and rate of improvement on acne lesions were substantially better on the side treated with a combination composition containing both the hydroxyacid and the antibiotic as compared to that of the antibiotic alone. The time for complete clearing of acne lesions treated with a combination composition varied from 4 to 12 weeks of time, with an average time of 8 weeks, whereas complete clearing with that of the antibiotic alone ranged from 8 weeks to 9 months, with an average of 4 months.

5. Preventing Hair Loss And For Hair Growth.

Prophylactic and therapeutic compositions containing minoxidil or dipyridamole with or without a hydroxyacid or related compound were provided to 6 human subjects having a progressive loss of hair on the scalp. Each participating subject received two medications; i.e. with or without the addition of a hydroxyacid to the composition containing minoxidil or dipyridamole. The subjects were instructed to apply topically one medication on one side of the scalp and the other medication on the other side of the scalp. Twice daily topical applications were continued for 2 to 6 months. Clinical evaluation shows that the combination compositions containing minoxidil or dipyridamole and a hydroxyacid or related compound were therapeutically more efficient in preventing the hair loss and enhancing hair growth on the scalp.

Therapeutic compositions containing clotrimazole or griseofulvin with or without the addition of a hydroxyacid were provided to 6 patients having recurrent fungal infections of the foot; i.e. athlete's foot with or without toe nail involvement. Each participating patient received two medications with or without the addition of a hydroxyacid to the composition containing clotrimazole or griseofulvin. The patients were instructed to apply topically one medication on one side of the body such as left foot, and the other medication on the other side of the body such as right foot. Three time daily applications were continued for one to two weeks. When nail infections were involved the topical application was continued for up to 4 months using the compositions containing griseofulvin with or without the addition of a hydroxyacid.

The degree and rate of improvement on skin lesions were clinically evaluated, and comparison was made one side of the body against the other. It was found that the skin lesions improved much faster with the compositions containing both the antifungal agent and the hydroxyacid. The presence of hydroxyacid appeared to enhance the efficacy of the antifungal agent, and also to eliminate the discomforts such as itching, tingling, burning and heat due to the fungal infection. Generally the infected skin healed within a week from topical application of the compositions containing an antifungal agent and a hydroxyacid. When toe nails were involved in the fungal infection the complete healing and regrowth of nails usually took several months on continued topical application of medications containing griseofulvin and a hydroxyacid.

The hydroxyacids and related compounds which may be useful as dermatologic agents for various conditions and disorders including age spots, keratoses, skin wrinkles etc. or as additives to enhance therapeutic effects of other cosmetic or pharmaceutical agents include 2-Hydroxyacetic acid; 2-hydroxypropanoic acid; 2-methyl 2-hydroxypropanoic acid; 2-hydroxybutanoic acid; phenyl 2-hydroxyacetic acid; phenyl 2-methyl

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2-hydroxyacetic acid; 3-phenyl 2-hydroxyacetic acid; 2,3-dihydroxypropanoic acid; 2,3,4-trihydroxybutanoic acid; 2,3,4,5,6-pentahydroxyhexanoic acid; 2-hydroxydodecanoic acid; 2,3,4,5-tetrahydroxypentanoic acid; 2,3,4,5,6,7-hexahydroxyheptanoic acid; diphenyl 2-hydroxyacetic acid; 4-hydroxymandelic acid; 4-chloromandelic acid; 3-hydroxybutanoic acid; 4-hydroxybutanoic acid; 2-hydroxyhexanoic acid; 5-hydroxydodecanoic acid; 12-hydroxydodecanoic acid; 10-hydroxydecanoic acid; 16-hydroxyhexadecanoic acid; 2-hydroxy-3-methylbutanoic acid; 2-hydroxy-4-methylpentanoic acid; 3-hydroxy-4-methoxymandelic acid; 4-hydroxy-3methoxymandelic acid; 2-hydroxy-2-methylbutanoic acid; 3-(2-hydroxyphenyl) lactic acid; 3-(4-hydroxyphenyl) lactic acid; hexahydromandelic acid; 3-hydroxy-3-methylpentanoic acid; 4-hydroxydecanoic acid; 5-hydroxydecanoic acid; aleuritic acid.

2-Hydroxypropanedioic acid; 2-hydroxybutanedioic acid; erythreric acid; threanic acid; arabiranic acid; ribaric acid; xylaric acid; lyxaric acid; glucaric acid; galactaric acid; mannaric acid; gularic acid; allaric acid; altraric acid; idaric acid; talaric acid; 2-hydroxy-2-methylbutanedioic acid.

Citric acid, isocitric acid, agaricic acid, quinic acid, glucuronic acid, glucuronolactone, galacturonic acid, galacturonolactone, uronic acids, uronolactones, ascorbic acid, dihydroascorbic acid, dihydroxytartaric acid, tropic acid, ribonolactone, gluconolactone, galactonolactone, guluronolactone, mannonolactone, citramalic acid.

Pyruvic acid, hydroxypyruvic acid, hydroxypyruvic acid phosphate, their esters; methyl pyruvate, ethyl pyruvate, propyl pyruvate, isopropyl pyruvate; phenyl pyruvic acid, its esters; methyl phenyl pyruvate, ethyl phenyl pyruvate, propyl phenyl pyruvate; formyl formic acid; its esters; methyl formyl formate, ethyl formyl formate, propyl formyl formate; benzoyl formic acid, its esters; methyl benzoyl formate, ethyl benzoyl formate and propyl benzoyl formate; 4-hydroxybenzoyl formic acid, its esters; 4-hydroxyphenyl pyruvic acid, its esters; 2-hydroxyphenyl pyruvic acid and its esters.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims and all changes which come within the meaning and equivalency of the claims are therefore intended to be embraced therein.

What is claimed is:

1. Method of visibly reducing a human skin wrinkle comprising topically applying to said wrinkle 2-hydroxypropanoic acid (lactic acid), or a topically effective salt thereof, in an amount and for a period of time sufficient to visibly reduce said wrinkle.

2. The method according to claim 1, wherein said 2-hydroxypropanoic acid is in the form of a free acid.

3. The method according to claim 1, wherein said 2-hydroxypropanoic acid is in salt form.

4. The method according to claim 1, wherein said 2-hydroxypropanoic acid or topically effective salt thereof is applied periodically for a period of time sufficient to achieve at least a clinically discernable reduction of said wrinkle.

5. The method according to claim 1, wherein said 2-hydroxypropanoic acid or topically effective salt thereof is applied periodically for a period of time suffi-

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cient to achieve at least a substantial eradication of said wrinkle.

6. The method according to claim 1, wherein said period of time is at least three months.

7. The method according to claim 1, wherein said period of time is at least four months.

8. The method according to claim 1, wherein said topical application is on a daily basis.

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9. The method according to claim 1, wherein said 2-hydroxypropanoic acid or topically effective salt thereof is present in a topically acceptable composition comprising a carrier.

10. The method according to claim 9, wherein said composition is a lotion, cream, gel, ointment or solution.

11. The method according to claim 1, wherein said topically effective salt is ammonium lactate.

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US005422370B1

REEXAMINATION CERTIFICATE (3272nd)**United States Patent [19]****[11] B1 5,422,370****Yu et al.****[45] Certificate Issued *Jul. 15, 1997**

[54] METHOD OF USING 2-HYDROXYPROPANOIC ACID (LACTIC ACID) FOR THE TREATMENT OF WRINKLES

[75] Inventors: Ruey J. Yu, Ambler; Eugene J. Van Scott, Abington, both of Pa.

[73] Assignee: Tristrata Technology, Inc., Wilmington, Del.

Reexamination Request:

No. 90/004,434, Oct. 28, 1996

Reexamination Certificate for:Patent No.: **5,422,370**Issued: **Jun. 6, 1995**Appl. No.: **179,189**Filed: **Jan. 10, 1994**

[*] Notice: The portion of the term of this patent subsequent to Feb. 25, 2009, has been disclaimed.

Related U.S. Application Data

[60] Continuation of Ser. No. 89,101, Jul. 12, 1993, which is a division of Ser. No. 8,223, Jan. 22, 1993, which is a continuation of Ser. No. 812,858, Dec. 23, 1991, abandoned, which is a continuation of Ser. No. 469,738, Jan. 19, 1990, abandoned, which is a continuation of Ser. No. 945,680, Dec. 23, 1986, abandoned.

[51] Int. Cl.⁶ A61K 31/19; A61K 7/48

[52] U.S. Cl. 514/557; 514/844; 514/847; 514/873

[58] Field of Search 514/557, 844, 514/847, 873

[56] References Cited**U.S. PATENT DOCUMENTS**

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FOREIGN PATENT DOCUMENTS

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Primary Examiner—James J. Seidleck

[57] ABSTRACT

A method for visibly reducing a skin wrinkle by topically applying to the wrinkle lactic acid or a topically effective salt thereof.

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**REEXAMINATION CERTIFICATE
ISSUED UNDER 35 U.S.C. 307**

NO AMENDMENTS HAVE BEEN MADE TO
THE PATENT

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AS A RESULT OF REEXAMINATION, IT HAS BEEN
DETERMINED THAT:
The patentability of claims 1-11 is confirmed.

* * * * *

CIVIL COVER SHEET

JS44

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by the Rules of Court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the Civil Docket Sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS**Tristrata Technology, Inc.**

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
EXCEPT IN U.S. PLAINTIFF CASES)
Leatherhead, Surrey, England

(c) ATTORNEYS FIRM NAME, ADDRESS AND PHONE NO.
Connolly Bove Lodge & Hutz LLP, 1007 N. Orange Street, PO Box
2207, Wilmington, DE 19899, Arthur G. Connolly, III, Esq., (302) 658-
9141

II. BASIS OF JURISDICTION

(PLACE AN "X" IN ONE BOX ONLY)

- | | |
|---|---|
| <input type="checkbox"/> U. S. Government Plaintiff | <input checked="" type="checkbox"/> Federal Question (U. S. Government Not A Party) |
| <input type="checkbox"/> U. S. Government Defendant | <input type="checkbox"/> Diversity (Indicate Citizenship of Parties in Item III) |

III. CITIZENSHIP OF PRINCIPAL PARTIES

(PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)

	PTF	DEF	PTF	DEF
Citizen of This State	<input checked="" type="checkbox"/> X1	<input type="checkbox"/> 01	Incorporated or Principal Place of Business in This State	<input type="checkbox"/> X4 <input type="checkbox"/> 04
Citizen of Another State	<input type="checkbox"/> 02	<input checked="" type="checkbox"/> X2	Incorporated and Principal Place of Business in Another State	<input type="checkbox"/> 05 <input checked="" type="checkbox"/> X5
Citizen or Subject of a Foreign Country	<input type="checkbox"/> 03	<input type="checkbox"/> 03	Foreign Nation	<input type="checkbox"/> 06 <input type="checkbox"/> 06

IV. ORIGIN

(PLACE AN "X" IN ONE BOX ONLY)

- | | | | | | | |
|---|---|--|---|--|---|--|
| <input checked="" type="checkbox"/> Original Proceeding | <input type="checkbox"/> Removed from State Court | <input type="checkbox"/> Remanded from Appellate Court | <input type="checkbox"/> Reinstated or Reopened | <input type="checkbox"/> Transferred from Another District (specify) _____ | <input type="checkbox"/> Multidistrict Litigation | <input type="checkbox"/> Appeal to District Judge from Magistrate Judgment |
|---|---|--|---|--|---|--|

V. NATURE OF SUIT (PLACE AN "X" IN ONE BOX ONLY)

CONTRACT	TORTS	PERSONAL INJURY	FORFEITURE/PENALTY	BANKRUPTCY	OTHER STATUTES
<input type="checkbox"/> 110 Insurance	PERSONAL INJURY	<input type="checkbox"/> 362 Personal Injury - Med. Malpractice	<input type="checkbox"/> 610 Agriculture	<input type="checkbox"/> 422 Appeal	<input type="checkbox"/> 400 State Reapportionment
<input type="checkbox"/> 120 Marine	<input type="checkbox"/> 310 Airplane	<input type="checkbox"/> 365 Personal Injury - Product Liability	<input type="checkbox"/> 620 Other Food & Drug	<input type="checkbox"/> 443 Withdrawal	<input type="checkbox"/> 410 Antitrust
<input type="checkbox"/> 130 Miller Act	<input type="checkbox"/> 315 Airplane Product Liability	<input type="checkbox"/> 366 Asbestos Personal Injury Product Liability	<input type="checkbox"/> 625 Drug Related Seizure of Property 21 USC 881	28 USC 157	<input type="checkbox"/> 430 Banks and Banking
<input type="checkbox"/> 140 Negotiable Instrument	<input type="checkbox"/> 320 Assault, Libel & Slander	<input type="checkbox"/> 370 Other Fraud	<input type="checkbox"/> 630 Liquor Laws	PROPERTY RIGHTS	<input type="checkbox"/> 450 Commerce/ICC Rates/etc.
<input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgment	<input type="checkbox"/> 330 Federal Employers' Liability	<input type="checkbox"/> 371 Truth in Lending	<input type="checkbox"/> 640 R.R. & Truck	<input type="checkbox"/> 820 Copyrights	<input type="checkbox"/> 460 Deportation
<input type="checkbox"/> 151 Medicare Act	<input type="checkbox"/> 340 Marine	<input type="checkbox"/> 380 Other Personal Property Damage	<input type="checkbox"/> 650 Airline Regs.	<input type="checkbox"/> 830 Patent	<input type="checkbox"/> 470 Racketeer Influenced and Corrupt Organizations
<input type="checkbox"/> 152 Recovery of Defaulted Student Loans (Excl. Veterans)	<input type="checkbox"/> 345 Marine Product Liability	<input type="checkbox"/> 385 Property Damage Product Liability	<input type="checkbox"/> 660 Occupational Safety/Health	<input type="checkbox"/> 840 Trademark	<input type="checkbox"/> 810 Selective Service
<input type="checkbox"/> 153 Recovery of Overpayment of Veteran's Benefits	<input type="checkbox"/> 350 Motor Vehicle	<input type="checkbox"/> 386 Other Personal Injury	<input type="checkbox"/> 690 Other	SOCIAL SECURITY	<input type="checkbox"/> 850 Securities/commodities/ Exchange
<input type="checkbox"/> 160 Stockholders' Suits	<input type="checkbox"/> 355 Motor Vehicle	<input type="checkbox"/> 390 Other Personal Product Liability	<input type="checkbox"/> 710 Fair Labor Standards Act	<input type="checkbox"/> 861 HIA (1395f)	<input type="checkbox"/> 875 Customer Challenge 12 USC 3410
<input checked="" type="checkbox"/> 190 Other Contract	<input type="checkbox"/> 360 Other Personal Injury	<input type="checkbox"/> 410 Voting	<input type="checkbox"/> 720 Labor/Mgmt. Relations	<input type="checkbox"/> 862 Black Lung (923)	<input type="checkbox"/> 891 Agricultural Acts
<input type="checkbox"/> 195 Contract Product Liability	CIVIL RIGHTS	<input type="checkbox"/> 442 Employment	<input type="checkbox"/> 730 Labor/Mgmt. Reporting & Disclosure Act	<input type="checkbox"/> 863 DIWC/DIWW (405(g))	<input type="checkbox"/> 892 Economic Stabilization Act
REAL PROPERTY	<input type="checkbox"/> 443 Housing/ Accommodations	<input type="checkbox"/> 444 Welfare	<input type="checkbox"/> 740 Railway Labor Act	<input type="checkbox"/> 864 SSID Title XVI (405(g))	<input type="checkbox"/> 893 Environmental Matters
<input type="checkbox"/> 210 Land Condemnation	<input type="checkbox"/> 445 Other Civil Rights	<input type="checkbox"/> 446 Other Civil Rights	<input type="checkbox"/> 750 Other Labor Litigation	<input type="checkbox"/> 865 RSI (405(g))	<input type="checkbox"/> 894 Energy Allocation Act
<input type="checkbox"/> 220 Foreclosure			<input type="checkbox"/> 791 Empl. Ret. Inc. Security Act	FEDERAL TAX SUITS	<input type="checkbox"/> 895 Freedom of Information Act
<input type="checkbox"/> 230 Rent Lease & Ejectment				<input type="checkbox"/> 870 Taxes (U.S. Plaintiff or Defendant)	<input type="checkbox"/> 900 Appeal of Fee Determination Under Equal Access to Justice
<input type="checkbox"/> 240 Torts to Land				<input type="checkbox"/> 871 IRS - Third Party 28 USC 7609	<input type="checkbox"/> 950 Constitutionality of State Statutes
<input type="checkbox"/> 245 Tort Product Liability					<input type="checkbox"/> 890 Other Statutory Actions
<input type="checkbox"/> 290 All Other Real Property					

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE.

DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY) 35 U.S.C. § 100, et seq - willful and deliberate Infringement

VII. REQUESTED IN COMPLAINT:

DEMAND \$ Damages and Injunctive relief

CHECK YES only if demanded in complaint:

CHECK IF THIS IS A CLASS ACTION
 UNDER F.R.C.P. 23JURY DEMAND: YES NO**VIII. RELATED CASE(S) IF ANY** (See instructions) Tristrata Technology, Inc. v. Milbar Laboratories, Inc., C.A. No. 05-801 (JJF); Tristrata Technology, Inc. v. Louise Bianco Skin Care Inc., et al., C.A. No. 06-644; Tristrata Technology, Inc. v. Jeunique International, Inc., et al., C.A. No. 06-645

DATE: October 20, 2006

SIGNATURE OF ATTORNEY OF RECORD *Arthur G. Connolly III*

(#2667)

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RECEIPT # _____ AMOUNT _____

APPLYING IFFP _____

JUDGE _____

MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44

Authority for Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdiction be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS-44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause.

V. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

VI. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS-44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 06-653

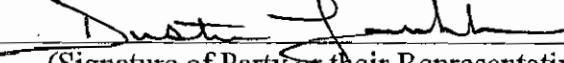
ACKNOWLEDGMENT
OF RECEIPT FOR AO FORM 85

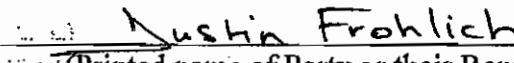
NOTICE OF AVAILABILITY OF A
UNITED STATES MAGISTRATE JUDGE
TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 1 COPIES OF AO FORM 85.

OCT 20 2006

(Date forms issued)


(Signature of Party or their Representative)


(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action